http://dx.doi.org/10.5588/ijtld.21.0024

Determinants of non-adherence to anti-TB treatment in high income, low TB incidence settings: a scoping review

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Article submitted 21 January 2021. Final version accepted 23 February 2021.

SUMMARY

BACKGROUND: Improving adherence to anti-TB treatment is a public health priority in high-income, low incidence (HILI) regions. We conducted a scoping review to identify reported determinants of non-adherence in HILI settings.

METHODS: Key terms related to TB, treatment and adherence were used to search MEDLINE, EMBASE, Web of Science, PsycINFO and CINAHL in June 2019. Quantitative studies examining determinants (demographic, clinical, health systems or psychosocial) of non-adherence to anti-TB treatment in HILI settings were included.

RESULTS: From 10,801 results, we identified 24 relevant studies from 10 countries. Definitions and methods of assessing adherence were highly variable, as were documented levels of non-adherence (0.9–89%). Demographic factors were assessed in all studies and clinical factors were frequently assessed (23/24). Determinants commonly associated with non-adherence were homelessness, incarceration, and alcohol or drug misuse. Health system (8/24) and psychosocial factors (6/24) were less commonly evaluated.

CONCLUSION: Our review identified some key factors associated with non-adherence to anti-TB treatment in HILI settings. Modifiable determinants such as psychosocial factors are under-evidenced and should be further explored, as these may be better targeted by adherence support. There is an urgent need to standardise definitions and measurement of adherence to more accurately identify the strongest determinants.

KEY WORDS: tuberculosis; adherence; treatment; determinants

Despite the availability of effective, low-cost medication, TB remains a global health concern.[1] One reason for this is non-adherence to anti-TB treatment, which increases morbidity and mortality,[2,3] transmission, the development of drug resistance and health disparities.[4–6] We have yet to identify the best adherence support for anti-TB treatment. Directly observed therapy (DOT) has been recommended by the WHO since the 1990s,[7] but research has not consistently found DOT to be superior to self-administered therapy (SAT) in reducing adverse treatment outcomes such as loss to follow-up.[8,9] Furthermore, improved outcomes from DOT dissipate when patients receiving SAT have increased contact with healthcare services,[8] suggesting that the benefit of DOT may result from the "encounter" rather than the "observation". This is important as DOT is resource-intensive, and can be perceived negatively by patients.[10–12]

Interventions to support adherence are more likely to be effective if they address the specific causes of non-adherence relevant to the individual patient.[13,14] Identifying specific, and potentially modifiable, determinants of adherence to anti-TB treatment is therefore critical for developing more targeted and effective support.[15]

Improving anti-TB treatment adherence is a priority for high-income, low TB incidence (HILI) countries progressing toward TB elimination.[16] To date, determinants have mostly been examined in high-incidence regions.[17–19] Determinants in high- and low-incidence regions may differ, based on differences in populations with TB and resources for care.[20–22] Therefore, as formative research for an intervention to promote adherence to anti-TB treatment in the United Kingdom,[23] we undertook a scoping review to explore determinants of non-adherence to anti-TB treatment within HILI settings, and identify evidence gaps relevant to patients and healthcare providers to be addressed by future research.

METHODS

We selected a scoping review methodology to provide a broad overview and highlight key evidence gaps,[24] given expectations of study heterogeneity[25,26] and diverse definitions and measurements of TB treatment adherence.[27] The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension Checklist for Scoping Reviews (PRISMA-ScR) was used.[25]

Literature search

Five databases (MEDLINE, EMBASE, Web of Science, PsycINFO and CINAHL) were searched in June 2019. Researchers developed and refined search terms related to TB, treatment, and adherence, with support from an experienced librarian (Supplementary Data I).

Search terms were mapped to the Population-Concept-Context framework recommended for scoping reviews (Table 1).[28] Identified studies were imported into Endnote[29] and duplicates were removed. Two authors (AJ and NB) independently screened titles and abstracts using the website Rayyan, designed for article screening in reviews.[30] Any discrepancies were resolved through discussion. Reference lists of included studies were manually searched to identify additional relevant studies.

Eligibility criteria are listed in Table 1. Included studies were peer-reviewed, English language studies using primary, observational, quantitative data on determinants of non-adherence to anti-TB treatment in countries classified as high-income[31] with low TB incidence rates (<40 per 100,000 population), when the study was conducted. We included outcomes of both discontinuation (early cessation of treatment, including loss to follow-up) and suboptimal implementation (missing doses during treatment).[32–34] We excluded qualitative research, as our research group has reviewed this separately (Arakelyan et al., article in submission).

Data extraction and synthesis

Two authors (AJ and NB) independently extracted data (cross-checking 50% of studies). Determinants were included if studied as primary exposures of interest or potentially confounding factors. Determinants were labelled as demographic, clinical, health systems or psychosocial. Categorises were used to reflect the strength of evidence for each determinant. A proxy measure was created for this, based on the size and direction of the effect size (ES) estimate and statistical certainty. Evidence was classified from strongest to weakest using the following categories: Category 1 (strongest): ES (ratio) ≥1.5, $P \leq 0.05$; Category 2: ES (ratio) ≥1.5, $P > 0.05$, small sample size ($n < 154$), i.e., study likely to be under-powered; Category 3: ES (ratio) >1.0 to <1.5, $P \leq 0.05$; and Category 4 (weakest): ES (ratio) >1.0, $P > 0.05$.

The equivalent categories were used to classify determinants observed to have a protective effect. In order to provide a standardised classification for Category 2, a sample size calculation was required. It was calculated that a minimum of 154 participants would indicate an adequately powered sample size, using 90% power and 5% significance level, statistically conservatively assuming that 50% of individuals had the outcome among the unexposed, and assuming a one-to-one ratio of exposed to unexposed or cases to controls. Although this threshold did not perfectly reflect the analyses in all studies, it provided a framework for weighting the evidence of each determinant. It did not indicate judgement on the quality of included studies. Where possible, determinants were classified based on ES in multivariable, not univariable, analyses.

Ethics

Ethics approval was not required as this was a scoping review.

RESULTS

Description of included studies

The initial search found 10,801 studies. After removing duplicates, 9932 remained for title and abstract screening, and 25 met the inclusion criteria (Figure 1, Supplementary Data II). Data on determinants were extracted for 24 studies, as one reported no ES.[35]

Included studies were published from 1986 to 2019 from 10 different countries, including the United Kingdom and Ireland (n = 7),[37–43] United States (n = 6)[35,43–47] and Spain (n = 5).[48–52] The most common study design was retrospective cohort (n = 12).[36,39,45,47,48,52–58] Sample sizes ranged from 62 to 73,591 (median: 1009, interquartile range [IQR] 184–2576). The mean/median participant age ranged from 28.0 to 52.1 years. The median percentage of males was 64.4% (IQR 56.0–71.0).

Most studies (n = 20) included all patients starting treatment in a given setting.[35–44,46,47,49–51,53–57] Three studies sampled specific high-risk groups, of people experiencing homelessness or unstable living arrangements,[59] individuals with multidrug-resistant TB (MDR-TB)[58] or HIV-TB co-infection.[52] Two studies compared outcomes between groups within a cohort, such as immigrants vs. individuals born within a country.[45,48]

Non-adherence: definitions and assessment

Supplementary Data II shows the considerable variability in definitions of adherence. Most study outcomes (n = 15) related to treatment discontinuation (stopping treatment early).[37,39,43–46,48,49,52–55,57–59] Fewer study outcomes (n = 7) appeared to record suboptimal implementation (missed doses during treatment).[35,36,38,40,42,47,56] One study included both a discontinuation and suboptimal implementation outcome.[41] Two studies used a single outcome comprising both discontinuation and suboptimal implementation.[50,51] Discontinuation outcomes were often measured using state or national registries/surveillance databases,[39,43–46,52–54,57,58] hospital/laboratory records[43,44,46,48,58] or medical notes.[37,59]

Suboptimal implementation was assessed using various methods, including adherence scale scores,[35] medical records,[56] physician impression from interviews/assessments,[38,40] patient self-report,[38] health visitor reports (including pill counts),[40] urine samples (to detect rifampicin),[38,42] attendance at appointments[40,47,56] and prescription requests.[47,56]

Overall, retrospective studies most often used surveillance/registry data to determine adherence,[36,39,44–46,52–54,57,58] whereas prospective studies used more varied methods (Supplementary Data II). Reported non-adherence ranged from 0.9% to 89% across studies (median 7.0%, IQR 5.2–16.3). Two studies did not report levels of non-adherence.[35,59]

Determinants of non-adherence

Demographic determinants

Demographic determinants were assessed by all 24 studies (Supplementary Data II). Specifically, the most studied determinant groups were place of residence and age (Supplementary Data III). The variable with the greatest strength of evidence for a large effect on non-adherence (Categories 1 or 2, i.e., large ESs with $P \leq 0.05$ or a small sample size, see Methods; Supplementary Data II) was place of residence (Figure 2). Within that variable, homelessness[36,41,43,45–47,49,52,56,59] and living in an institution or prison (e.g., a "confined institution", a residence hall or mental hospital)[36,41,45,46,50,51,54,57] had the strongest evidence, weighted overall, towards non-adherence (Supplementary Data II).

Age, sex, ethnicity and nationality also showed mixed evidence of effects, as within each variable just as many or more studies found a weak effect with non-adherence as a large effect (Figure 2). Ethnicity and nationality determinants appeared very context-specific, as indicated by the variation in baseline comparators within these categories. Overall, few

demographic determinants were classified in Categories 2 (i.e., large ES, $P > 0.05$, but small sample size) or 3 (small ES, $P \leq 0.05$) in terms of strength of evidence. The grouping variables most commonly found to have a weak effect on adherence (Category 4, small ES, $P > 0.05$) were age, nationality/origin and ethnicity. No variable had a consistently large effect with non-adherence.

Clinical determinants

Clinical determinants were the second most studied category (23/24 studies Supplementary Data II). The substance use/misuse grouping variable was the most frequently assessed and had the most evidence weighted towards a large effect (Supplementary Data III and Figure 2). Specifically, illicit drug misuse/addiction had the strongest evidence for this (Supplementary Data II).[47,49–51,54] The evidence for clinical determinants was also mixed, in terms of both strength of evidence and direction. For example, in the HIV grouping variable, HIV-positive status was a risk factor for non-adherence,[49,50,54] yet a diagnosis of AIDS (acquired immune deficiency syndrome) was protective against non-adherence (Supplementary Data IV).[43,45] Again, few determinants fell into Categories 2 and 3 in terms of strength of evidence, and the grouping variables which most commonly showed a weak effect with adherence were smear and sputum result, substance use/misuse and HIV infection.

Health systems determinants

Health systems determinants were less frequently investigated (8/24 studies). Within this category, route to care was the most studied grouping variable (Supplementary Data III). Healthcare professionals' perception of patient understanding (e.g., lack of awareness of TB severity, understanding of treatment instructions, language barriers) had a consistently large effect with non-adherence, although this determinant was minimally studied. The grouping variables most often found to have a weak effect with adherence were route to care, and those classified as "other".

Psychosocial determinants

Psychosocial determinants were the least studied (6/46 studies), where only mental health and having close relationships were assessed (Supplementary Data III, Figure 2). Of these, having

a mental health problem was both a risk for[41] and protective against non-adherence (Supplementary Data II).[46] Strength of evidence for mental health problems was also mixed, with as many studies finding strong and weak effects on adherence.

DISCUSSION

In our scoping review investigating the determinants of non-adherence to anti-TB treatment within HILI settings, homelessness, incarceration, and alcohol or drug misuse were commonly associated factors. Health systems and psychosocial determinants were under-explored. Considerable heterogeneity in measurements and definitions of non-adherence was present across studies, hindering the conclusions that can be drawn.

When synthesising the literature on determinants, we found that demographic and clinical factors were most studied. This may reflect the relative ease of capturing this data through TB surveillance in HILI settings, such as the United Kingdom.[60] However, the context required to understand mixed findings for these determinants was largely missing from studies, which may result from utilising these data sources. Without context, these findings are unhelpful for explaining non-adherence. For example, a recent systematic review found that despite assumptions, non-adherence was as likely to occur in both migrants and non-migrants.[61] Such findings highlight the importance of contextualising demographic and clinical determinants, if researchers are to utilise this data in intervention design.

In addition, demographic and clinical determinants are largely non-modifiable (e.g., history of incarceration) or difficult to change (such as homelessness, illicit drug use/ addiction) within a feasible, scalable healthcare intervention.[62] Improving adherence to anti-TB treatment requires identifying potentially modifiable determinants that can be targeted within a pragmatic, person-centred healthcare intervention.

Determinants more amenable to change, such as health systems issues, have rarely been quantitatively assessed in HILI settings. Health systems barriers in high-incidence regions, such as distance to treatment facilities and transport costs,[16-18] may be less apparent in HILI countries with better-resourced health services. Nonetheless, they may affect subgroups of patients, given that TB disproportionately affects people with lower socio-economic status in high-income settings.[19] In addition, health systems determinants may

interact with other factors (such as fear of stigma making an individual seek care at a more distant hospital), reinforcing the need to better understand their influence in HILI settings.

Psychosocial determinants are also under-researched in quantitative literature on TB adherence. This oversight is significant given the known relationship between TB, stigma and adherence, even in low-incidence settings.[63] Understanding the social context of TB treatment is significant for reaching TB control goals, given the well-established links between social determinants of health and inequality,[64] even within regions of low TB incidence.[65]

Theory in behavioural medicine suggests adherence is best viewed as a modifiable behaviour and not a trait,[66] as adherence patterns can change within an individual over time,[31,67] and also differ between people with shared demographic characteristics. Theory and evidence suggest that amendable, cognitive and affective factors, such as beliefs about illness and treatment, influence subsequent coping strategies, including treatment adherence.[68–70] Understanding psychosocial determinants may enable us, therefore, to provide better adherence support.

Evidence from this review has important clinical implications for intervention development in TB. Interventions should 1) accurately assess known risk factors for non-adherence to anti-TB treatment in HILI settings; and 2) mitigate the influence of these on perceptual and practical barriers to adherence.[69] For example, interventions should be tailored to both target a patient's beliefs about TB and treatment, and provide practical support to overcome personal barriers to treatment.

Our scoping review followed PRISMA-ScR guidelines to systematically search the available literature. We may have been limited by only including English language studies. We may have missed secondary data reported (e.g., in intervention studies) by only including studies whose primary aim was to examine determinants of non-adherence. In addition, as this was a scoping review, the quality of included studies was not assessed.

Our understanding of non-adherence to anti-TB treatment within HILI settings is severely limited by the heterogeneity of included studies. Clearer and consistent definitions of which type of non-adherence is being assessed in studies,[32] and data presented beyond simple binary summary measures, are urgently needed.[71]

By including all data on reported determinants, whether measured as primary exposures of interest or potential confounding factors, some estimates may be subject to bias. Of note, few (n = 2) studies assessed all four categories of determinants and therefore adjusted for confounders appropriately. This considerably impairs our ability to understand the interaction between determinants and their relationship to non-adherence, and may explain the inconsistency of the included evidence.

In conclusion, this scoping review identifies determinants with the best supportive evidence, and highlights a gap in our understanding of adherence to anti-TB treatment in HILI settings. Understanding how demographic and clinical determinants are associated with adherence to anti-TB treatment is necessary to inform intervention development. Qualitative work could extend current understanding by examining how health systems and psychosocial factors influence anti-TB treatment in HILI settings.[22] Stakeholders in TB policy and service implementation should also consider how factors influencing patient adherence are currently evaluated and understood. Existing care practices, such as risk assessments, should ensure the range of complex factors involved in adherence are comprehensively addressed.

We also identified a need for greater consistency in definitions and measurement of adherence within the TB literature. Without this, it will remain difficult to effectively synthesise data, and understand reported patterns of adherence behaviour.

Acknowledgements

This work was supported by the National Institute for Health Research (NIHR; London, UK) Health Technology Assessment Programme (UK grant number 16/88/06). The views expressed are those of the authors and not necessarily those of the National Health Service, UK, the NIHR or the Department of Health and Social Care. HRS is funded by the Medical Research Council (MRC; London, UK) (MR/R008345/1).

Conflict of interests: ASK reports grants from the National Institute for Health Research (London, UK), during the conduct of the study; personal fees from The Aurum Institute (Johannesburg, South Africa), The Center for Health Policies and Studies (Chisinau, Republic of Moldova), Edanz Group (Fukuoka, Japan), Vital Strategies (Singapore), University of Cape Town (Cape Town, South Africa), the Bill & Melinda Gates Foundation (Seattle, WA, USA) and Bloomberg Philanthropies (New York, NY, USA) outside the

submitted work; non-financial support from Kyoto University (Kyoto, Japan) and the Africa Health Research Institute (Durban, South Africa) outside the submitted work. CNJC reports personal fees from Public Health England (PHE; London, UK) outside the submitted work. HRS reports grants from Medical Research Council (London, UK) and the NIHR during the conduct of the study; from Korean CDC (Seoul, Korea) and Johnson and Johnson (New Brunswick, NJ, USA) and other from Latvian Society Against Tuberculosis (Riga, Latvia) outside the submitted work; and HRS is a core group member of the World Health Organization's European Tuberculosis Research Initiative and co-chair of UK Academics and Professionals Against Tuberculosis. KK, MCIL, and MD report grants from the NIHR during the conduct of the study. RH is supported by the NIHR (Collaboration for Leadership in Applied Health Research and Care, North Thames at Bart's Health NHS Trust and Asthma UK (AUKCAR). Speaker engagements with honoraria with the following companies: Abbvie (North Chicago, IL, USA), Amgen (Thousand Oaks, CA, USA), Astellas (Chuo City, Tokyo, Japan), AstraZeneca (Cambridge UK), Biogen (Cambridge, MA, USA), Erasmus (Rotterdam, The Netherlands), Idec (Osaka, Japan), Gilead Sciences (Foster City, CA, USA), GlaxoSmithKline (Brentford, UK), Janssen (Beerse, Belgium), Merck Sharp Dohme (Kenilworth, NJ, USA), Novartis (Basel, Switzerland), Pfizer (New York, NY, USA), Roche (Basel, Switzerland), Shire Pharmaceuticals (Lexington, MA, USA) and TEVA (Petah Tikva, Israel). RH is founding director of a University College London-Business spin-out company (Spoonful of Sugar Ltd, London, UK) providing consultancy on treatment engagement and patient support programmes to healthcare policy makers, providers, and industry. FBW is an employee of PHE. All other authors declare no conflicts of interest.

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Table (PCC) elements and inclusion/exclusion criteria

PCC element	Definition in scoping review	Inclusion criteria	Exclusion criteria
Population	Patients taking anti-TB treatment	Studies reporting data on non-adherence to treatment for pulmonary TB	• Studies with a non-human sample • Studies with patients taking prophylactic TB treatment or treatment for latent TB • Studies where the majority of patients (>50%) had extra-pulmonary disease • Studies with a comorbid sample (excluding HIV)
Concept	Determinants of non-adherence to treatment	Peer-reviewed studies reporting primary, observational, data on determinants of non-adherence to treatment	• Studies reporting interventions (including studies where DOT/VOT were standard treatment, or more than 50% of the sample was receiving DOT/VOT) • Qualitative studies • Studies that were not primary research articles (e.g., reviews, commentaries or letters) • Studies that did not measure determinants of non-adherence • Studies where treatment completion was the outcome (as this is conflated with successful treatment outcome and is not a measure of patient adherence)
Context	High-income, low (TB) incidence settings	Countries classified as high-income and low TB incidence at time of study	Studies in settings defined as low and middle income, or with high TB incidence

PCC = patient-concept-context; DOT = directly observed therapy; VOT = video-observed therapy.

FIGURE LEGENDS

Figure 1. PRISMA diagram of screening process and included studies. PRISMA = Preferred Reporting Systematic Reviews and Meta-Analyses.

Figure 2. Determinants of non-adherence to TB treatment. Bars may include multiple determinant levels assessed within the same study. Darkest grey indicates the strongest effect (i.e., Category 1: a large risk or protective effect at $P < 0.05$), medium grey indicates a large risk or protective effect at $P > 0.05$ with a small sample size (Category 2), light grey indicates a small risk or protective effect at $P < 0.05$ (Category 3) and lightest grey indicates the weakest effect found at $P > 0.05$ (Category 4). HCP = healthcare professional; SES = socio-economic status.

Figure 1.

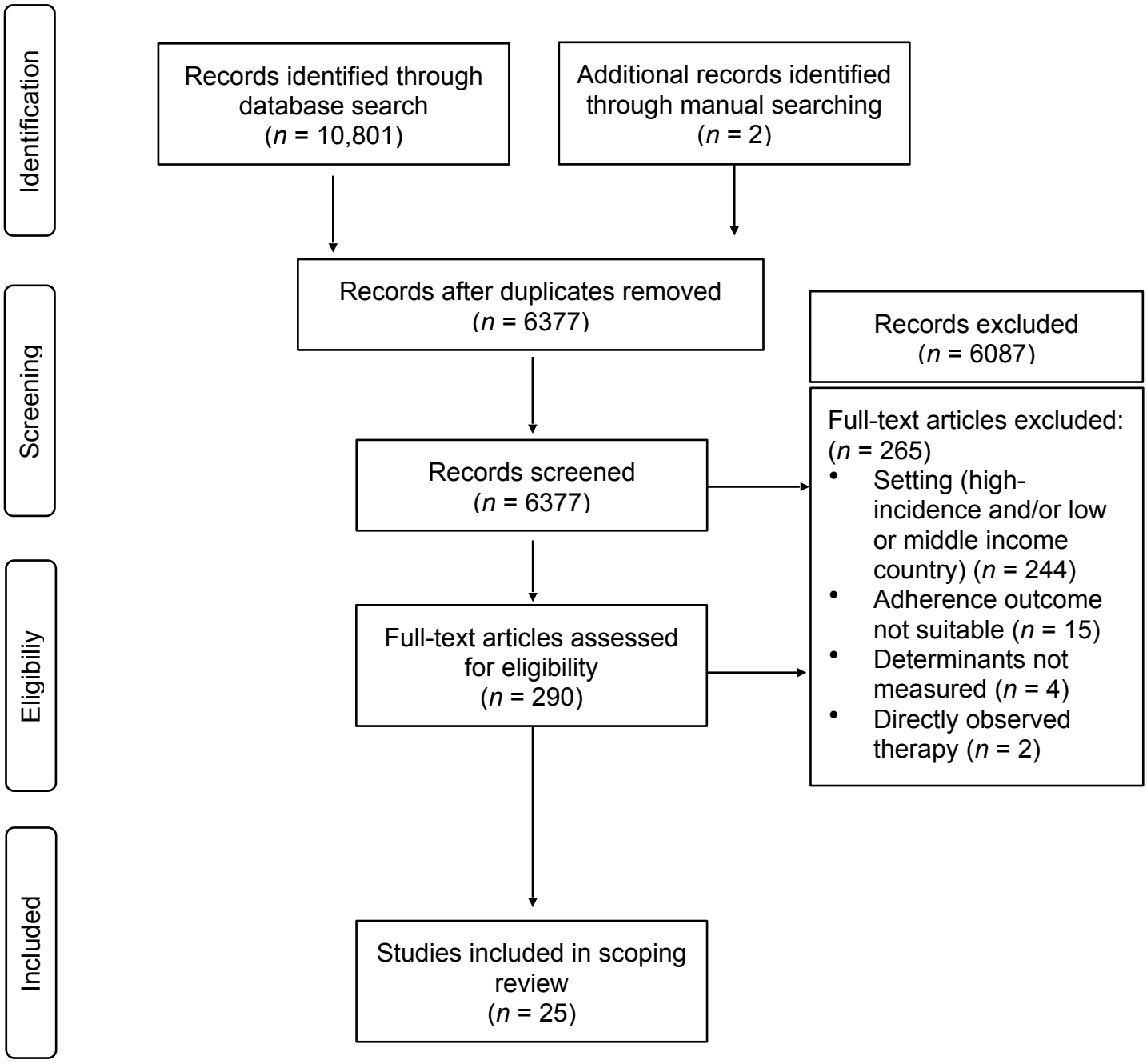
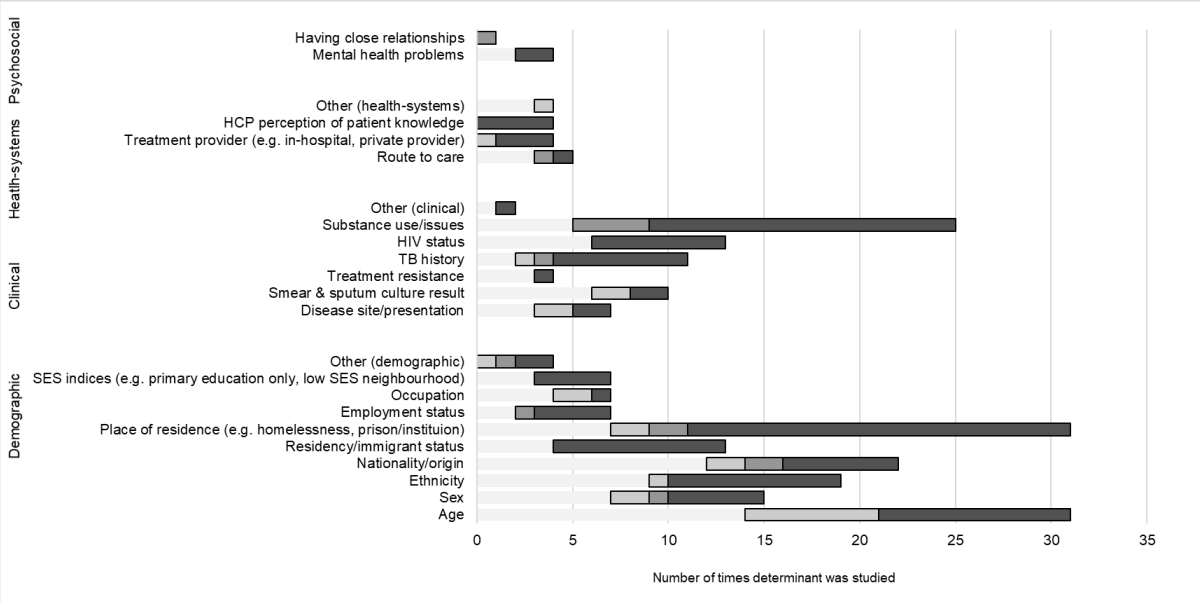

Identification
Screening
Eligibiliy
Included
Records identified through database search (n = 10,801)
Additional records identified through manual searching (n = 2)
Records after duplicates removed (n = 6377)
Records excluded (n = 6087)
Records screened (n = 6377)
Full-text articles excluded: (n = 265)
Setting (high-incidence and/or low or middle income country) (n = 244)
Adherence outcome not suitable (n = 15)
Determinants not measured (n = 4)
Directly observed therapy (n = 2)
Full-text articles assessed for eligibility (n = 290)
Studies included in scoping review (n = 25)

Figure 2


Psychosocial
Health-systems
Clinical
Demographic
Having close relationships
Mental health problems
Other (health-systems)
HCP perception of patient knowledge
Treatment provider (e.g. in-hospital, private provider)
Route to care
Other (clinical)
Substance use/issues
HIV status
TB history
Treatment resistance
Smear & sputum culture result
Disease site/presentation
Other (demographic)
SES indices (e.g. primary education only, low SES neighbourhood)
Occupation
Employment status
Place of residence (e.g. homelessness, prison/instituion)
Residency/immigrant status
Nationality/origin
Ethnicity
Sex
Age
0
5
10
15
20
25
30
35
Number of times determinant was studied

RÉSUMÉ