Translational Behavioral Medicine

Barriers, facilitators and interventions for medication adherence across chronic conditions with the highest non-adherence rates: A scoping review with recommendations for intervention development

--Manuscript Draft--

Manuscript Number:	TBMP-D-20-00141R1
Full Title:	Barriers, facilitators and interventions for medication adherence across chronic conditions with the highest non-adherence rates: A scoping review with recommendations for intervention development
Article Type:	Original Research
Keywords:	Medication Adherence; barriers; Psychological Interventions; Chronic Conditions; Scoping Review
Abstract:	Background: Medication non-adherence (MNA) constitutes a complex health problem contributing to increased economic burden and poor health outcomes. The Medication Adherence Model (MAM) supports that numerous processes are involved in medication adherence (MA). Purpose: Based on the MAM and guidelines of the World Health Organization (WHO), this scoping review aimed to identify the barriers and facilitators associated with MA, and the behavioral health interventions and techniques among chronic conditions presenting with high non-adherence rates (asthma, cancer, diabetes, epilepsy, HIV/AIDS, hypertension). Methods: PubMed, PsycINFO and Scopus databases were screened, and 243 studies were included. A mixed methods approach was used to collate the evidence and interpret findings. Results: The most commonly reported barriers to MA across conditions were: younger age, low education, low income, high medication cost, side effects, patient beliefs/perceptions, comorbidities, and poor patient-provider communication. Additionally, digitally delivered interventions including components such as medication and condition education, motivational interviewing (MI), and reinforcement and motivational messages led to improvements in MA. Conclusions: This review highlights the importance of administrating multicomponent interventions digitally and personalized to the patients' individual needs and characteristics, responding to the adherence barriers faced. This is the first review examining and synthesizing evidence on barriers and facilitators to MA and behavioral health interventions used for improving MA across chronic conditions with the highest non-adherence rates and providing recommendations to researchers and clinicians. Stakeholders are called to explore methods overcoming barriers identified and developing effective multicomponent interventions that can reduce the high rates of medication non-adherence.
Response to Reviewers:	On behalf of the author team, I would like to thank you for giving us the opportunity to revise and resubmit our work to Translational Behavioral Medicine. We would also like to thank the reviewers for their comments, which we believe have greatly improved our manuscript. Below you can find a detailed response to all reviewers' comments. Changes relating to reviewer comments in the manuscript were done using yellow highlight color for ease of identification. Reviewer #1: 1) Abstract-Purpose "Based on the MAM..." not to As the reviewer correctly identified, this was a typo and was corrected as suggested. 2) Implications - when discussing interventions may want to add "behavioral health" somewhere so that intervention term is specific to behavior change; think about changing "fear" to concerns. The intervention term was changed to specify "behavioral health" interventions throughout the manuscript. We have retained both terms 'fear' and 'concerns' as both were mentioned in the included papers as such so to emphasize that both can be patient-related barriers to medication adherence. 3) P. 4 - can you provide one more example of an intervention (e.g. CBT.....) As suggested, one more intervention example was added. We also made an effort to provide more broad examples of interventions based on social cognitive models like the Theory of Planned Behavior:

	‘Behavioral health interventions are based on psychotherapeutic approaches (e.g., Cognitive Behavioral Therapy [CBT], Acceptance and Commitment Therapy [ACT]) or other social and cognitive models (e.g. Theory of Planned Behavior)…’ 4) p.5- when say "synthesizing evidence for barriers; can add facilitators here too? The emphasis is on the barriers which are many, however, it would be optimal if spoke about facilitators too and this would be throughout the paper Based on the reviewer’s suggestion, the term “facilitators” was added in page 5. This was also changed throughout the paper and we ensured that the paper focus was on both barriers and facilitators to MA. 5) p. 8 - The characteristics addressed make it clear that more studies have been in done in some areas more than others, can you add a discussion point in the Discussion about that discrepancy and the need for more representation of all chronic illnesses reviewed? Discussion points were added regarding this discrepancy of examination of barriers, facilitators and interventions in some conditions more than others. In particular, relevant information was added in the Discussion sections: “Barriers and Facilitators across Conditions” and “Characteristics of Identified Interventions”. 6) p.10 - there is a brief paragraph on facilitators separate from the barriers, just wondering if might be better integrated throughout? Also, would be good if could add more on family as a facilitator in Discussion points As suggested, facilitators were integrated throughout the Results section “Barriers and Facilitators to MA” and other parts of the manuscript. In addition, the impact of family support to higher medication adherence was added and further described in the Discussion sections: “Barriers and Facilitators across Conditions” and “Using Barriers and Facilitators in Behavioral Health Intervention Development”. 7) p.12- could you define term "health literacy"? As suggested, a definition was added in the first paragraph of page 15: “…i.e., poor understanding of basic health information and services; [38]” 8) p.13 - when discussing characteristics of identified behavioral interventions can you comment on patient-provider communication and family support? Based on the reviewer’s suggestion, discussion on the impact of the family support and patient-provider communication as intervention components was added particularly in the Discussion. 9) p.15- consider adding a short paragraph on digital versus in person interventions A paragraph on digital versus in person interventions was added in the Discussion. 10) p.15- sentence saying "directly address barriers and mechanisms - would add barriers, facilitators, and mechanisms; also consider specifying "interventions" with behavioral health interventions As suggested, this change was made. Also, the term “interventions” was changed into “behavioral health interventions” throughout the paper. Reviewer #2: This scoping review summarizes literature on medication nonadherence in patients who have one of several chronic diseases for which medication nonadherence is most common. The findings are structured around the WHO framework of factors that affect nonadherence. The authors call for multicomponent interventions to address common barriers. The methods are straightforward and the tables detailed. In this reviewer's opinion, however, the authors have not taken an approach or generated a conclusion that advances current knowledge in this field. Indeed, the findings and conclusions are identical to that of many other systematic reviews. The cited ways in which this review differs from others are not compelling. What is needed is a more critical examination of the problems with existing studies to generate actionable plans for moving the field forward. This is missing from this report. Thank you for this important comment and for allowing us to edit the manuscript so to make a stronger effort to express how we aim to advance current knowledge in the field. This was exactly our argument when designing this study: that the literature has been critically evaluated but we needed a mapping technique to collate evidence from diverse studies which is exactly the purpose of scoping reviews. We think that by following your recommendations we are now making it clearer what this scoping review offers beyond what is currently known throughout the paper. For example, this is the first paper to examine barriers and facilitators utilizing the WHO dimensions examining them across those chronic conditions that reportedly are found to have the highest medication non-adherence rates. It is also the first to link these with behavioral health

	intervention findings on how to combat MNA and provides recommendations for both researchers and clinicians who are interested in helping improve MA. Thus this scoping review presented and analyzed gaps in knowledge and identified areas where future researchers and clinicians can take off and also translate for policymaking work. Major comments 1) There are many directions this review could take to try to push the field forward, a few of which will be mentioned. The authors provide a list of barriers to adherence but have not addressed the fact that some are not modifiable or would be difficult (logistically if not ethically) to intervene on, such as younger age or lower education or income. What attempts have been made to intervene on patients with these characteristics? Citing these barriers also seems to put the blame on patients with these characteristics without asking what healthcare providers and policy can do to facilitate adherence for these patients. This is a very important point and we are in total agreement with the reviewer. We have now added in the Discussion to highlight this issue as well as explaining why it is important to know that non-modifiable factors impact adherence. Based on the reviewer's suggestion, we have also explained in more detail in Discussion section "Using Barriers and Facilitators in Behavioral Health Intervention Development" what attempts can be made to differently intervene in characteristics and sociodemographic factors that are not modifiable and are associated with higher MNA. Additionally, recommendations to healthcare providers and policymakers were added to facilitate adherence even in cases when barriers are non-modifiable. Please see particularly the Discussion section "Using Barriers and Facilitators in Behavioral Health Intervention Development" and in Appendix I. 2) The authors note in the Discussion that medication adherence costs should be reduced, but that will not happen any time soon, at least not in the US. What, then, can be done to improve adherence among patients who cannot afford medications? There is literature on this issue in many areas such as pharmacy and medicine. This is indeed important and we agree on the point about costs of medication. More recommendations and relevant literature were added in the Discussion section "Using Barriers and Facilitators in Behavioral Health Intervention Development". "We recognize that medication costs can not necessarily be reduced in many parts of the world, thus when possible, healthcare providers may distribute free samples, help patients access medication discounts, and prefer combination therapies vs. multiple medications [49]." 3) The authors do not distinguish between multi component and single component interventions. Historically many interventions have taken a one-size-fits-all approach, addressing only a single barrier to adherence. Many authors have written about this and suggested that interventions need to be able to address varying (both between and within persons) reasons for nonadherence. Another way of moving this field forward would be discuss nonadherence among patients with multiple chronic conditions. Most patients with diabetes also have hypertension. Is studying adherence in each disease as a silo the way to do this? We agree with the reviewer and we definitely wanted to make the case as suggested. We added information and description of multi-component and single component interventions in the Results section "Behavioral Health Interventions and Techniques Used for MA": "Multicomponent interventions (n=36, 64.3%) were mostly administrated followed by single component interventions (n=20, 35.7%). The most common multicomponent interventions were reminders plus educational/reinforcement/motivational messages (n=15, 28.8%), motivational interviewing (MI; n=7, 12.5%) and CBT (n=4, 7.1%). Single component interventions included reminders (n=11, 19.6%), education on condition and medication (n=5, 8.9%) and reinforcement/motivational messages (n=4, 7.1%)." We also highlighted these points in the discussion section. Furthermore, as the reviewer correctly recommends, a way of moving this field forward is to discuss nonadherence among patients with multiple chronic conditions. This was one of our aims (see section "The Present Study"); however, this was not possible as only one study was included with patients with multiple chronic conditions (i.e., diabetes and hypertension). Therefore, this was further described and added as a suggestion for future researchers in the Discussion section "Characteristics of Identified Interventions": "It is evident from this review that there is a discrepancy and a need for interventions targeting several chronic conditions, especially asthma and cancer. Furthermore, current research is limited to the study of single conditions at a time, when comorbidity

	is common (e.g., diabetes coexisting with hypertension). In our review, no studies were included with patients with comorbid conditions, thus more research is needed in regards to MA in individuals with multiple chronic conditions." 4) Finally, the authors have not addressed the issue of medication adherence measurement. At first blush it may seem unrelated, but this reviewer feels otherwise. The widely varying estimates of adherence (7-95% for hypertension alone!) is due at least in part to poor measurement. With poor measurement, identifying patients who need intervention, and evaluating effects of interventions, cannot be done with a high level of confidence. It is unclear how these cited studies have measured barriers and intervened on them. Thanks for your comment and we are totally in agreement regarding the issue of MA measurement. Information on how the included studies measured adherence was added in the Results section "Article Characteristics". In addition, in the first paragraph of the Discussion section we address the issue of heterogeneous medication adherence measurement in included studies and we added the comment as suggested by the reviewer. Also, in Appendix I we provide recommendations on the assessment of medication adherence for improving adherence. Minor comments 5) The literature review seems incomplete. This reviewer is aware of trials that have attempted to improve nonadherence that included adherence as a primary or secondary outcomes, yet they are not included (a few examples of relevant investigators are Kronish, Bosworth, and Ogedegbe). Thank you for this suggestion. We understand that it is always possible to miss studies and what is included depends on the keywords used and inclusion and exclusion criteria. We decided early on to include only studies where medication adherence was a primary outcome, and this information we ensured to be clearly explained in the Method section "Study Selection". Yet, we did double check our included studies and did not identify others that we missed. Some of the studies commented on by the reviewer were considered but did not fulfill the inclusion criteria such as the examined chronic conditions were not the ones associated with the highest MA rates. Yet, two of the included studies have Dr. Ogedegbe as an author suggesting that this teams' work has been included in our investigation. Data of the screening procedure are available in Open Science Framework (OSF) in https://osf.io/b3xe7/. 6) When the authors draw inferences about adherence rates from the literature, are they using baseline values for randomized trials? This would seem appropriate but is not stated. Yes, we have used the baseline values from all studies including randomized trials. We have added this information in the Results section "Article Characteristics" and in the first paragraph in the Discussion section. 7) The authors mention that having children is a facilitator of adherence but have not explained why. In the HIV literature, having children can both facilitate and impede adherence. Several systematic reviews and writings by investigators have addressed this issue in depth. As the reviewer correctly presents, there is HIV-related literature supporting that having children can act both as a barrier and facilitator to MA. We have added this literature, with a number of reasons underling this finding and recommendations in the Discussion section "Barriers and Facilitators across Conditions". 8) Digital intervention is a mode of delivery. The authors combine it with intervention content. It would be important to determine intervention components that might lead to adherence, and a separate question is how to deliver those components. What are the text messages trying to achieve? Which barriers are they targeting, and which behavior change techniques? As correctly suggested, we have distinguished the mode of delivery from intervention content throughout the paper. Additionally, we have added and clearly explained which intervention components are effective and their delivery mode in the Results section "Behavioral Health Interventions and Techniques Used for MA". Reviewer #3: The authors clearly put a great deal of work into this manuscript, going far beyond typical background reading for a single study. The authors attempt to evaluate multi-level barriers and facilitators to medication adherence across multiple conditions and treatments and in multiple populations (individual, societal, and structural characteristics), in quantitative and qualitative studies, with multiple designs (observational and experimental), and evaluate intervention strategies for improving adherence across all of these factors.

	We would like to thank the reviewer for recognizing the great deal of work which we have put in this manuscript. My main concern is that this manuscript attempts to do too much, so that insufficient attention is given to each research question encapsulated by this review to strongly contribute to the literature. The authors have gained an understanding of the existing research done on predictors of medication adherence, but the information provided in this review doesn't provide "actionable" information, that other researchers could build from—for either narrowing focus for future research (i.e., to identify causal mechanisms of non-adherence) or selecting intervention strategies. Thank you for the comment and we recognize that a scoping review may often seem to try to do many things. We do recognize this, but we also think that because of the diversity of the literature in this field in terms of research design and measurement methods (among others), a broad scoping review can provide information useful for future research. We have attempted to ensure that findings from this review provide actionable information for research, clinical practice and policymaking. We think the reviewer's comment on suggesting future researchers to narrow down the focus to the causal mechanisms of non-adherence is important, and we have provided this suggestion in the Discussion. 1) Regarding the former (identifying causal mechanisms of non-adherence): the review does not provide a unifying theory that helps to synthesize the existing evidence to better understand potential causal factors. The reader only knows what generally predicts adherence from a pool of factors that others have studied. For example, younger age (under 30) was associated with poorer adherence, but the reader isn't any closer to knowing why. Is it because younger adults hold different beliefs than older adults, that the medications taken by younger adults are different in their barriers (cost, side effects) than those taken by older adults, or that younger adults with chronic illness have lower levels of education than older adults with chronic illness (etc)? The method doesn't seem rigorous enough to even conclude that younger age is a consistent barrier to adherence, because there wasn't a targeted analysis of the conditions in which age is more/less influential on adherence. Nor is there an analysis of the relative importance of different factors, since none of the reviewed studies evaluated all of the proposed factors (and this review is not a meta-analysis). Perhaps if the MAM theory is used to drive the synthesis rather than the WHO framework. Thanks for your comment. Based on the reviewer's suggestion, we have added relevant information in the Discussion section "Barriers and Facilitators across Conditions", explaining where possible why some factors are associated with higher non-adherence rates. However, this was not the objective of this review and we have provided the rationale why a scoping review was preferred because the emphasis was to examine and clarify key definitions in the literature, identify types of available evidence and key characteristics of factors, and analyze gaps in knowledge. Scoping review was also preferred as we sought to inform practice in the field and the way the research has been conducted (Munn et al., 2018). As suggested by the reviewer we have provided a guidance for future research in synthesizing the causal mechanisms of MNA because we think this is very important. We agree that some of the questions posed by the reviewer would better be answered with a meta-analysis, but we think this would be a next step to what we aimed to do with this paper. Additionally, the WHO framework was preferred to drive the synthesis of the focus of the scoping review into translational evidence to practice rather than updating theoretical evidence (which is the purpose of a systematic review and where a theory like MAM would be more appropriate). The WHO framework clearly explains, organizes and categorizes the factors associated with medication adherence (see Introduction section "Barriers associated with MNA") and we mapped the evidence into this categorization. 2) Regarding the latter (intervention strategies), the reader learns from this review what others have tried but not how each strategy works relative to others, for particular conditions and populations. Whether a provider/researcher works with a specific population and a specific condition or multiple conditions and a diverse population, there isn't enough evidence to narrow down their intervention strategy options. As suggested, more information was added providing information on which intervention strategies work across and for particular chronic condition, in the Results section "Behavioral Health Interventions and Techniques Used for MA". For example: "Overall, most of the included studies delivered interventions digitally (n=38, 67.9%), followed by face-to-face (n=13, 23.2%) and both delivery modes (n=5, 8.9%).

	Multicomponent interventions (n=36, 64.3%) were mostly administrated followed by single component interventions (n=20, 35.7%). The most common multicomponent interventions were reminders plus educational/reinforcement/motivational messages (n=15, 28.8%), motivational interviewing (MI; n=7, 12.5%) and CBT (n=4, 7.1%). Single component interventions included reminders (n=11, 19.6%), education on condition and medication (n=5, 8.9%) and reinforcement/motivational messages (n=4, 7.1%).” Also, in the Discussion section “Characteristics of Identified Interventions”: “Clinicians and especially those working with patients with HIV/AIDS and diabetes, should prefer using a combination of reminders with messages including motivation, psychoeducation and CBT techniques than reminders alone. Other effective interventions for patients with HIV/AIDS included CBT and problem-solving techniques.” “Interventions involving family members and improving the communication between the patient and the healthcare provider and system are of particular importance as most interventions target patients without involving their social and medical support systems [1, 25, 36].” 3) As the authors present, medication adherence and non-adherence are complex topics and multi-determined. The causes of non-adherence and the strategies for improving adherence likely depend on the condition, the population (including individual characteristics and social and structural characteristics), and the treatment. A more targeted analysis of adherence factors and intervention strategies is warranted. Barriers to medication adherence and intervention strategies across and for particular conditions were added in the Results sections “Barriers and Facilitators to MA”: [example]: “When conditions were also examined separately, a commonly reported barrier in studies including patients with HIV/AIDS consisted of greater alcohol consumption. Regarding facilitators to MA, common socioeconomic-related factors across conditions included higher education level, higher socioeconomic status, having children, good social support, and presence of family members who take care and remind them to take medications.” and “Behavioral Health Interventions and Techniques Used for MA”: “Overall, most of the included studies delivered interventions digitally (n=38, 67.9%), followed by face-to-face (n=13, 23.2%) and both delivery modes (n=5, 8.9%). Multicomponent interventions (n=36, 64.3%) were mostly administrated followed by single component interventions (n=20, 35.7%). The most common multicomponent interventions were reminders plus educational/reinforcement/motivational messages (n=15, 28.8%), motivational interviewing (MI; n=7, 12.5%) and CBT (n=4, 7.1%). Single component interventions included reminders (n=11, 19.6%), education on condition and medication (n=5, 8.9%) and reinforcement/motivational messages (n=4, 7.1%).” Also, a discussion of these findings was added in Discussion sections “Barriers and Facilitators across Conditions” and “Characteristics of Identified Interventions”. 4) It is possible that much greater detail in support of each research question/conclusion could strengthen the contribution of this manuscript. As it is, the reader is left to wade through complex Appendices in order to see the original data and/or to blindly accept the authors' interpretation of the qualitative and quantitative literature. Some more specific examples: in the Discussion, the authors claim that the wide variation (4 to 98%) in non-adherence "can be attributed to the type of design…, to the heterogeneity in measurement methods, and in how individuals who are non-adherent are identified"—why are these factors highlighted and not others, such as type of condition, age of participants, and type of treatment, among other non-adherence factors? What evidence leads the authors to conclude this? Another example, the authors state that "higher prevalence of MNA in patients with lower education levels…[is] probably associated with a poorer understanding of the healthcare providers' instructions…"—this is a speculation on the part of the authors and not robustly evidenced by the data. The issue isn't that the authors are wrong, since it is entirely plausible that low education predicts low adherence through poor understanding of the treatment, etc, but this review doesn't provide evidence to support this claim. I applaud the authors' incredible effort at attempting to accomplish very important tasks for the field. I think to make a useful contribution to the literature, this review and its many objectives require greater rigor and narrower focus in analysis. We understand and we agree that readers should not have to wade through Appendices to see the original data. We have made an effort to strengthen the Results section (please also see responses to other reviewers’ comments) as well as the Discussion section. However, we also needed to account for the page limitations of the journal so that was the reason we provide the more detailed data from the studies in

	the Appendices. We do hope that now more information is provided with examples from the studies to strengthen our conclusions. Based on the reviewer's recommendations, a narrower focus in analysis was made supporting each research question/conclusion in order to strengthen the contribution of this manuscript with information added throughout Results and Discussion sections. For example: "When conditions were also examined separately, a commonly reported barrier in studies including patients with HIV/AIDS consisted of greater alcohol consumption." "When conditions were also examined separately, in studies including patients with asthma, poor knowledge on how to use the inhaler was commonly reported, whereas in patients with diabetes and hypertension poly-pharmacy was reportedly associated with MNA." "It is worth mentioning that these components were mostly delivered digitally through SMS/text messages (e.g., reminders, condition and medication education, motivation), targeting the barriers of forgetfulness and health illiteracy on condition and medication. Furthermore, MI resulted in significant improvements of MA when delivered in any mode." "Certain barriers relating to socioeconomic characteristics, such as younger ages, low education and income, may not be modifiable, however interventions can differentially target these groups and the particular mechanisms that contribute to MNA. Multicomponent behavioral interventions including techniques of CBT, MI, and problem-solving combined with reminders may be effective in young adults [16, 44]. To maximize the benefits of an intervention, the social support system of the patient including providers and family members should be assessed and involved if so desired by the patient [25, 36]. Healthcare providers are advised to use clear and simple language avoiding medical jargon, especially in patients with lower education levels [45]. Additionally, in order to engage younger adults in treatment, providers can incorporate technological aspects such as videos, and promote the participation in online forums interacting with individuals with similar experiences [46]." In addition, we have added more evidence supporting our arguments for the two examples reported by the reviewer, in the first paragraph of Discussion and in the first paragraph of page 14. Specifically, for the factors underlying the variability of medication adherence rates as well as why lower education levels are associated with lower medication adherence.

Implications (explicitly state the impact of the findings for researchers, practitioners, and policymakers; ONE SENTENCE

Implications

Practice: Tailored, multicomponent, and empirically supported interventions based on patients' personalized barriers are advised in order to help patients adhere to their prescribed medication.

Policy: Policymakers who want to decrease barriers related to fears or concerns regarding medication use should adopt a patient-centered approach to treatment, where patients in collaboration with health care providers make shared decisions on medication management, discuss concerns and resolve fears.

Research: Future research is needed to examine interventions targeting the various WHO dimensions of medication non-adherence, and especially what will work for whom, under which conditions and whether the effects can be long-lasting.

Barriers, facilitators and interventions for medication adherence across chronic conditions with the highest non-adherence rates: A scoping review with recommendations for intervention development

Abstract

Background: Medication non-adherence (MNA) constitutes a complex health problem contributing to increased economic burden and poor health outcomes. The Medication Adherence Model (MAM) supports that numerous processes are involved in medication adherence (MA). **Purpose:** Based on the MAM and guidelines of the World Health Organization (WHO), this scoping review aimed to identify the barriers and facilitators associated with MA, and the behavioral health interventions and techniques among chronic conditions presenting with high non-adherence rates (asthma, cancer, diabetes, epilepsy, HIV/AIDS, hypertension). **Methods:** PubMed, PsycINFO and Scopus databases were screened, and 243 studies were included. A mixed methods approach was used to collate the evidence and interpret findings. **Results:** The most commonly reported barriers to MA across conditions were: younger age, low education, low income, high medication cost, side effects, patient beliefs/perceptions, comorbidities, and poor patient-provider communication. Additionally, digitally delivered interventions including components such as medication and condition education, motivational interviewing (MI), and reinforcement and motivational messages led to improvements in MA. **Conclusions:** This review highlights the importance of administrating multicomponent interventions digitally and personalized to the patients' individual needs and characteristics, responding to the adherence barriers faced. This is the first review examining and synthesizing evidence on barriers and facilitators to MA and behavioral health interventions used for improving MA across chronic conditions with the highest non-adherence rates and providing recommendations to researchers and clinicians. Stakeholders are called to explore methods overcoming barriers identified and developing effective multicomponent interventions that can reduce the high rates of medication non-adherence.

Keywords: Medication Adherence; Barriers; Behavioral health Interventions; Chronic Conditions; Scoping Review

Introduction

Medication adherence (MA) is the extent to which patients take their medication as recommended by their healthcare provider [1]. Rates of medication non-adherence (MNA) are comparable between patients receiving short- and long-term therapies, but it constitutes a more serious problem for patients with chronic treatment courses as it results in health deterioration, treatment failure, healthcare cost increases, and worse quality of life [2]. Chronic conditions are health problems/diseases with long duration (more than three months) or are persistent with slow progression [3]. Chronic conditions having the highest rates of MNA include: asthma, cancer, diabetes, epilepsy, HIV/AIDS, and hypertension [1, 4]. Studies with patients in routine care present higher MNA rates compared to clinical trials (see Appendix A). Therefore, MNA is a global, multi-determined, and complex health problem, contributing to increased morbidity, economic burden, and poor health outcomes [2]. It is thus of paramount importance to understand the barriers associated with MNA and interventions and techniques currently used to improve it.

Examining common MA barriers, facilitators and interventions across chronic conditions is essential given they are highly co-morbid [5, 6] with patients taking multiple medications and as a result, intentionally or unintentionally changing their prescribed regimen, experiencing medication interactions, and having frequent inpatient admissions [7]. The Medication Adherence Model (MAM) [14] describes the processes involved in MA and supports three core contributing concepts: 1) Purposeful action, where the decision to adhere depends on perceived effectiveness and need of the regimen; 2) Patterned behavior, referring to establishing medication-taking patterns like daily routines; 3) Feedback, referring to patients evaluating their medication-taking using prompts and information. Based on MAM, barriers to MNA relate to these concepts which if altered can reinforce the need to maintain or modify medication-taking. For example, 25% of

adults in Netherlands, and 55% and 80% of elderly in Australia and Canada respectively, have three or more chronic conditions and 88% are prescribed at least one medication [5, 6]. Evidence on commonalities of MA across conditions may provide more valuable information for clinicians, policymakers and the health system than reviews on each condition separately [8–13].

MNA is a multidetermined complex phenomenon, and this is reflected in mixed and heterogeneous findings of previous reviews examining barriers [8, 12, 13, 15–18]. Several factors are reportedly associated with MNA and range from intentional (e.g., deciding to omit a dose) to unintentional (e.g., forgetfulness) [14]. The World Health Organization (WHO) [1] organized and summarized the various factors positively or negatively associated with MNA that can be translated to actions into five dimensions: 1) Socio-economic; 2) Factors related to health-care teams and systems; 3) Condition-related; 4) Therapy-related; and 5) Patient-related factors. Mapping the evidence from the literature on factors associated with MNA into the WHO framework can contribute to translating into policymaking actions and interventions.

Behavioral health interventions are based on psychotherapeutic approaches (e.g., Cognitive Behavioral Therapy [CBT], Acceptance and Commitment Therapy [ACT]) or other social and cognitive models (e.g. Theory of Planned Behavior) aiming to change health-related behaviors and improve functioning and well-being. Some evidence suggests that such behavioral interventions [12, 19–21] especially when digitally delivered [17, 22] present with effectiveness and improve MA. Generally, the interventions included in these reviews are diverse and the targeted populations vary in demographics, health conditions targeted, and sample sizes.

The aim of this review is to provide the scope of the problem, map and compile lessons learnt from the literature regarding barriers and facilitators of, as well as behavioral health interventions for MA in patients with various chronic conditions [23, 24]. This is the first review

to: a) examine evidence for barriers and facilitators to MA (based on and including all dimensions recommended by WHO) across chronic conditions with the highest MNA rates; b) investigate the effectiveness of behavioral health interventions for improving MA; and c) provide recommendations to researchers and clinicians.

Previews reviews examining barriers, facilitators and interventions to MA: 1) reported on conditions irrespective of whether they present with high rates of MNA, 2) examined MA related factors without consideration of known dimensions (e.g., as presented by WHO), thus, having less policy relevance, and 3) focused mostly on a single health condition at a time ignoring comorbidities [11–13, 15, 19, 25, 26]. As a result, it is difficult to develop a program theory of change to apply in health systems or replicate and confirm evidence which are not consistently operationalized. By synthesizing evidence for barriers, facilitators and intervention outcomes and providing recommendations for intervention development based on these factors, researchers and clinicians can more effectively address MA. A scoping review was preferred to a systematic review as it allows for the examination and clarification of key definitions in the literature, identifying key characteristics of MNA, and presenting and analyzing gaps in knowledge [23, 24, 27].

Methods

Procedure

The review was registered with PROSPERO (registration number: CRD42019134371) and followed PRISMA guidelines for scoping reviews [28]. Data supporting the findings of this study are available in Open Science Framework (OSF) in https://osf.io/b3xe7/ (DOI 10.17605/OSF.IO/B3XE7).

Relevant studies (no data restrictions applied) were identified by searching PubMed, PsycINFO and Scopus databases. Searches were conducted until March 2020. Existing relevant

meta-analyses and reviews were also examined for additional eligible studies. Search terms based on title and abstract, included: “medication adherence”, “medication intake”, “medication concordance” and “medication compliance”. For the full search strategy see Appendix B.

Published and unpublished (e.g., dissertations) peer-reviewed studies of chronic conditions recognized as having significant MNA according to WHO [1] with MA explicitly stated as the primary or secondary outcome were eligible for selection. Samples had to be comprised of participants over 18 years and diagnosed with asthma, cancer, diabetes, epilepsy, HIV/AIDS, hypertension or any combination of these conditions. Eligible studies needed to report any barrier, facilitator, or behavioral health intervention or technique addressing MA or MNA as a primary outcome based on either self-report or other instruments (e.g., pill counts, electronic measurements).

To identify barriers and facilitators associated with MNA, studies needed to: a) report any barrier to MA: socioeconomic-related, health-care team and system factors, condition-related, therapy-related and patient-related factors, and b) use qualitative (i.e., interview, focus groups) or quantitative (i.e., randomized controlled trial, correlational, experimental and causal-comparative) research methods. To identify behavioral interventions and techniques tackling MNA, studies needed to: a) use a quantitative research method comparing an intervention group with control or, if lacking a control group, to have utilized a design with pre-post intervention comparisons, and b) report any behavioral health intervention or technique (e.g., reminders, etc.). Studies were excluded if they were: a) published in language other than English, b) case studies and reviews, and c) examining MA on psychiatric disorders or comorbidities of the chronic condition with psychiatric disorders.

Articles were screened for eligibility by the first author. At all stages, an additional author screened the studies and Inter Rater Reliability (IRR) was assessed using Cohen's kappa [29]. Almost perfect agreement was observed between the two screeners in title-abstract (IRR=97%; k=.93) and substantial agreement in full-text screening (IRR=89%; k=.73). Any discrepancies were resolved in consensus meetings with the research team.

A data charting form was used to enter the extracted data. From all included studies, a mixture of general information about the study and specific information relating to the aims of this scoping review were extracted (see Appendix C).

Data Synthesis

A narrative synthesis [30, 31] was used to provide descriptive information, summarize and explain included study findings. This narrative synthesis described study characteristics, participants' MA, barriers, facilitators, and interventions and techniques used to improve MA for each of the six included chronic conditions. A mixed methods framework was used to synthesize the quantitative and qualitative studies' data; i.e., a convergent synthesis design, where both data types are collected and analyzed at the same time [30]. Based on type of data provided by each study, the results-based convergent synthesis design was also used (i.e., quantitative and qualitative data were analyzed and presented separately and then discussed together). Statistical information was extracted from the quantitative studies whereas main themes or categories were extracted from qualitative studies.

Results

Article Characteristics

A total of 243 records were included from full-text screening (see Figure 1 for a detail procedure and reasons for exclusion). Characteristics and references of the included studies are

presented in Appendices D and E, respectively. Included studies were published between 1995 and 2020, with the majority conducted in the USA (*n*=75, 30.9%). Specifically, 187 addressed barriers and facilitators of MA and 56 examined MA interventions. Most of the included studies implemented a cross-sectional design (*n*=130, 53.5%) and assessed MA in healthcare provision (*n*=180, 74.1%). Most, addressed MA in HIV/AIDS (*n*=114, 46.9%), followed by hypertension (*n*=53, 21.8%), diabetes (*n*=46, 18.9%), asthma (*n*=13, 5.4%), epilepsy (*n*=10, 4.1%), cancer (*n*=6, 2.5%), and combination of diabetes and hypertension (*n*=1, 0.4%). Based on baseline values provided by each study (including RCTs), the MA rates for HIV/AIDS varied from 18-98% (*M*=70.8%, *SD*=19.6), hypertension from 7-95% (*M*=60.5, *SD*=20.3), diabetes from 15-93% (*M*=54.5, *SD*=19.7), asthma from 4-89% (*M*=41.1, *SD*=26.7), epilepsy from 34-90% (*M*=61.8, *SD*=16.1), and cancer from 45-84% (*M*=63.2, *SD*=16.2).

Most studies assessed MNA using self-report methods (*n*=197, 81.1%) such as validated questionnaires (*n*=130, 66.0%). Yet, there was a diversity in how MA was assessed in included studies, with 34 different questionnaires been used and eight non-self-report measures. Most self-reports divided participants into categories: non-adherent vs. adherent (*n*=100, 50.8%). Other studies, assessing MA with non-self-reports (*n*=26, 10.7%) or a combination (*n*=20, 8.2%) defined mostly MNA as taking less medication than prescribed by providers (*n*=28, 60.9%).

Barriers and Facilitators to MA

Description of the barriers and findings of each study are presented in Appendix F (quantitative) and G (qualitative). Figure 2, presents the most commonly reported factors under each WHO dimension [1] across conditions examined.

Socioeconomic-related. Overall, most studies (*n*=153, 63.0%) examined socioeconomic-related barriers to MA. Across conditions, significant barriers were poor social support (e.g.,

family), younger age (e.g., less than 30), lower education level (e.g., high-school), low income, high medication cost, and access/location difficulties (e.g., living in rural locations). Qualitative exploration indicated that reasons underlining these factors included, lack of motivation to be adherent when family members are unhappy with the condition, and poor understanding of doctors' instructions related to education level. When conditions were examined separately, a common barrier in studies including patients with HIV/AIDS consisted of greater alcohol consumption. Regarding facilitators to MA, common socioeconomic-related factors across conditions included higher education level, higher socioeconomic status, having children, good social support, and presence of family members who take care and remind them to take medications.

Condition-related. Condition-related barriers (*n*=127, 52.3%) included: low condition health literacy, presence of comorbid illnesses (e.g., depression), family history, longer time since diagnosis, and absence of symptoms. Reasons behind these barriers from qualitative evidence included receiving little or no condition education from healthcare providers, feeling like a burden to family, and being adherent only when happy. Common factors relating to facilitators included, higher disease literacy and acceptance of diagnosis.

Therapy-related. Therapy-related barriers (*n*=144, 59.3%) across conditions included side effects, complex medication regimens, longer treatment duration, multi-medication use, and low literacy about medication. Qualitative exploration indicated barriers of, little medication education provided by pharmacists, interference of side effects to daily life, high frequency of dosing and food requirements, and great number of pills taken. When conditions were examined separately, commonly reported factors were, poor knowledge on how to use the inhaler in patients with

asthma, whereas in patients with diabetes and hypertension it was poly-pharmacy. Regarding facilitators to MA across conditions, only higher medication literacy was consistently reported.

Patient-related. Patient-related barriers (*n*=201, 82.7%) included: forgetfulness, fear/concerns about side-effects, negative perceptions/beliefs about medication (e.g., medications are undesirable, harmful), feeling better/healthy, lower self-efficacy, denial/stigma of diagnosis, and weaker beliefs in personal need for medication. From qualitative evidence barriers were: busy schedule, medication beliefs that they will limit patients' activities and cause damage to many body parts (e.g., heart failure, liver). Common facilitators to MA included: use of reminder tools, stronger beliefs on the necessity and efficacy of medication, and having goals in life. Qualitatively reported facilitators included: believing in the effectiveness of treatment and perception that they help to live longer.

Health-care team and system-related. Seventy-four (30.5%) studies examined health-care team and system-related barriers. Most commonly reported barriers across conditions were: dissatisfaction and lack of trust in services and clinicians, poor patient-provider communication, and unavailability of drugs. Reasons behind these barriers from qualitative evidence included being frustrated with healthcare providers as no or confusing instructions were provided. A common facilitator to MA across conditions included only the good patient-provider relationship.

Behavioral Health Interventions and Techniques Used for MA

Fifty-six included studies examined a behavioral health intervention or technique for combating MNA. More information on the specific interventions and techniques are available in Appendix H. Twenty-six studies focused on patients with HIV/AIDS, 12 with hypertension, 12 with diabetes, four with asthma, two with cancer, whereas none examined interventions for MNA in patients with epilepsy. MA was assessed in the majority of studies with self-reports only (*n*=34,

60.7%), whereas only 13 (23.2%) used more objective means and nine studies (16.1%) utilized a combination of assessment methods.

Overall, most studies delivered interventions digitally (*n*=38, 67.9%), followed by face-to-face (*n*=13, 23.2%) and both delivery modes (*n*=5, 8.9%). Most were multicomponent interventions (*n*=36, 64.3%), followed by single component interventions (*n*=20, 35.7%). Multicomponent interventions tended to include reminders plus educational/reinforcement/motivational messages (*n*=15, 28.8%), motivational interviewing (MI; *n*=7, 12.5%) and CBT (*n*=4, 7.1%). Single component interventions included reminders (*n*=11, 19.6%), education on condition and medication (*n*=5, 8.9%) and reinforcement/motivational messages (*n*=4, 7.1%). In most studies (*n*=47, 83.9%), interventions were administered for a period of six months or less.

Components of behavioral interventions that were reported as effective (based on improvements on MA rates) across conditions included: condition and medication education, importance of being adherent, and provision of reinforcement/motivational messages. These components were mostly delivered digitally through SMS/text messages (e.g., reminders, condition and medication education, motivation), targeting the barriers of forgetfulness and health illiteracy on condition and medication. Furthermore, MI resulted in significant improvements of MA when delivered in any mode. CBT and problem-solving techniques were effective across delivery modes, especially for patients with HIV/AIDS. Additionally, reminders showed a significant contribution to higher MA at post-treatment. However, in patients with HIV/AIDS and diabetes, a combination of reminders with messages including motivation, psychoeducation on condition and medication, and CBT techniques were more effective than reminders alone.

Discussion

In this review, a total of 243 studies were included providing a summary of evidence on the barriers and facilitators affecting MA in asthma, cancer, diabetes, epilepsy, HIV/AIDS, and hypertension (187 studies), as well as behavioral health interventions and techniques used for improving MA (56 studies). Based on the methods used to assess adherence, the prevalence of MA at baseline as reported by included studies across all chronic conditions examined varied widely (4% to 98%). This variation in rates of MA can be attributed to various mostly methodological reasons such as the type of design (clinical trial vs. healthcare), heterogeneity in measurement methods coupled with lack of a universally agreed-upon consensus measurement method and the variability in objective (e.g., pill counts) and subjective (e.g., self-report measures) means to assess MA, and ways in which individuals who are non-adherent are identified and classified (e.g., lower than a specified cutoff score, taking less than 85% of prescribed medication) [2, 32]. Given the poor measurement issues, identifying patients who need intervention and evaluating the effects of interventions cannot be done with a high level of confidence.

Barriers and Facilitators across Conditions

Common socioeconomic barriers to MA identified across conditions were younger age, high medication cost, low education, low income, access/location difficulties, and poor social support. Significant socioeconomic facilitators were, higher education, higher socioeconomic status, having children, and good social support. Although these barriers and facilitators are consistently found to be associated with MA across chronic conditions [12, 16, 17, 25, 33] it is important to highlight that these are not directly modifiable factors. However, knowing that these are related to MNA may help interventions like public health campaigns to be more targeted.

The lower rates of MA in younger patients may reflect beliefs or perceptions against medication, non-acceptance of condition and its treatment, or self-stigma [1]. Younger patients may be also less motivate to prioritize treatment over their social demands compared to older individuals [34]. In the future, researchers are advised to examine specific perceptions associated with younger ages. Another consistent finding is the higher prevalence of MNA in patients with lower education levels, probably associated with a poorer understanding of the healthcare providers' instructions and knowledge on the health condition, its implications and treatment [12]. Lower years of education are associated with poorer understanding of prescription instructions and medication terms related to the chronic condition [35].

Additionally, family support is consistently associated with MA both as a barrier and facilitator, suggesting the high impact that significant others and their beliefs/perceptions have for patients [1, 25, 36]. Therefore, if family members are supportive, they should be included in the intervention since they may positively impact MA and provide patients with medication taking assistance and reminders [33]. For patients who have children, their existence can aid in motivating patients to help themselves remain healthy and survive [33]. However, having children may become a barrier, as previously reported in some HIV studies, where competing child care responsibilities hinder MA [33, 37]. Further research is required to decipher under what conditions family members act as barriers as opposed to facilitators of MA.

Furthermore, individuals with low income might not afford their medications particularly when their cost is high, and as such have higher MNA rates [25]. The high impact of health illiteracy (i.e., poor understanding of basic health information and services; [38]) on MA is also evident in the condition- and therapy-related barriers and facilitators categories (see Appendix I for recommendations). Other commonly reported barriers included forgetfulness, fears/concerns

about medication side effects, and patient-provider communication. Regarding healthcare providers, their role is vital in MA [12, 13, 25, 39] and parameters hindering communication and thus impacting MA should be targeted via health behavior interventions. Poly-pharmacy was also associated with lower MA as observed in patients with comorbid diabetes and hypertension [5, 6]. Future studies are advised to examine factors associated with MA in patients with multiple chronic conditions, as most studies examined a single chronic condition ignoring comorbidities and possible polypharmacy. Additionally, MA, barriers, facilitators and interventions in certain conditions has been understudied, such as in cancer patients. Future studies should examine MA in these conditions bearing in mind comorbidities among conditions and the extra layers of barriers that this may bring.

Overall, our findings reflect what is proposed by the MAM theoretical framework [14]. Specifically, patients may become non-adherent because they perceive medications as detrimental to their health (e.g., beliefs/perceptions) or ineffective, they have not established a routine for remembering to take them (patterned behavior) and poor communication and in some cases poor support were presented as barriers to MAD [14]. Future research may consider narrowing the focus to identifying factors that may constitute causal mechanisms of MNA and to explore in depth providers' perceptions of these mechanisms.

Characteristics of Identified Interventions

Effective components of behavioral interventions (mostly digitally-delivered) across conditions included education, personalized motivational feedback, motivational interviewing, and reinforcement messages. Though reminders lead to improvements across conditions, additional components targeting the various barriers to MA are needed in order to achieve sustainable MA rates. Professionals, especially those working with patients with HIV/AIDS and

diabetes, should prefer using a combination of reminders with messages including motivation, psychoeducation, problem-solving and CBT techniques, than reminders alone.

Findings are in accordance to those of previous reviews [19–22, 40–42]. However, there remains a lack of well-controlled behavioral intervention studies addressing multiple barriers. The available multi-component interventions tend to be administered for a short duration, with the majority following patients for less than six months. Given the chronicity of these health conditions and their association with MNA [43], behavioral intervention outcomes need to be examined longitudinally across the course of the chronic condition. Especially for epilepsy, we were surprised at the dearth of studies examining effective interventions for MA. It is evident from this review that there is a discrepancy and a need for interventions targeting understudied chronic conditions, especially asthma and cancer. Furthermore, current research is limited to the study of single conditions at a time, when comorbidity is common (e.g., diabetes coexisting with hypertension). In our review, no studies were included intervening on MA for patients with comorbid conditions, presenting an area where more research is required. Moreover, lacking are behavioral interventions targeting the various dimensions of MNA (e.g., based on the WHO framework), and especially examining what will work for whom, under which conditions and whether the effects can be long-lasting. There is a great need for the development of interventions specifically designed to address multiple barriers to MA (instead of a one-size-fits-all approach addressing a single barrier to adherence) that are tailored and easy to access and use. Interventions involving family members and improving the communication between the patient and the healthcare provider and system are of particular importance as most interventions target patients without involving their social and medical support systems [1, 25, 36]. Once developed, it is

important to establish interventions' acceptability, effectiveness and efficacy across conditions and time.

Using Barriers and Facilitators in Behavioral Health Intervention Development

Specific barriers that contribute to MNA can constitute intervention targets (see Appendix I for recommendations based on findings). Certain barriers relating to socioeconomic characteristics, such as younger ages, low education and income, may not be modifiable, however interventions can differentially target these groups and the particular mechanisms that contribute to MNA. Multicomponent behavioral interventions including techniques of CBT, MI, and problem-solving combined with reminders may be effective in young adults [16, 44]. To maximize the benefits of an intervention, the social support system of the patient including providers and family members should be assessed and involved if so desired by the patient [25, 36].

Healthcare providers are advised to use clear and simple language avoiding medical jargon, especially in patients with lower education levels [45]. Additionally, in order to engage younger adults in treatment, providers can incorporate technological aspects such as videos, and promote the participation in online forums interacting with individuals with similar experiences [46]. Tailoring of behavioral interventions and developing interventions with user-engagement in mind are also advised [47]. Specifically, digitally delivered interventions hold promise for effectively combating MNA since almost all adults use a mobile phone [38]. They also have the advantage to be tailored to a person's individual characteristics, needs and preferences [19, 38], capitalizing on MA facilitators. Patients from remote areas and patients with low socioeconomic status who cannot afford paying for face-to-face interventions can be additionally reached [38]. However, providers should have in mind the disadvantages of digital interventions, including the absence of human interactions [48].

Healthcare systems should also aim to minimize or subsidize medication costs and offer alternative solutions (e.g., the choice of generic medications) or patient-assistance programs [43]. We recognize that medication costs can not necessarily be reduced in many parts of the world, thus when possible, healthcare providers may distribute free samples, help patients access medication discounts, and prefer combination therapies vs. multiple medications [49]. Furthermore, we recommend that healthcare practitioners should screen for parameters known to interfere with MA (e.g., screening for comorbidities [50]). Once risks for MNA are identified, specific behavioral interventions can be implemented such as condition and medication side-effects education, motivating patients about MA importance, and opening communication lines with healthcare providers and utilizing communication and problem-solving skills to discuss concerns and resolve fears.

Adopting a patient-centered approach to treatment, where patients are actively involved in decisions about their medication management and treatment can lead to a decrease in barriers related to fears or concerns regarding medication use [51]. For example, the UK NICE guidelines recommend that healthcare professionals increase the involvement of patients in the process of decision-making, acknowledge their views about their condition and treatment, and understand their knowledge, beliefs, and concerns about medications [52]. In accordance with the MAM framework, we recommend also that healthcare practitioners should in collaboration with patients examine the perceived effectiveness of suggested medications and help them initiate and establish a routine [14]. Such an approach can also influence and improve patient-provider communication and further impact MA.

Limitations

Firstly, certain findings should be interpreted with caution, such as those for cancer, epilepsy and asthma, due to the small number of studies identified and included. Secondly, there was high heterogeneity in definition and measurement methods of MA and included populations. Third, fifteen studies were not included as we were unable to access them, even after contacting corresponding authors. However, a large number of studies were included in the present review, representing the main topic in a sufficient way. Finally, this review was limited to English language studies, thus, we might have missed some relevant studies especially from non-English speaking low- and middle-income countries. However, 61 countries were represented in this review, with 104 studies from low- and middle-income countries included.

Conclusions

Behavioral and multicomponent interventions going beyond reminders are needed together with an expert consensus on MA definition and measurement methods. Before administrating an intervention, researchers should identify the function of the MNA behaviors of the patient, identify barriers and facilitators, so as to intervene appropriately. Modern psychosocial theories and behavioral interventions (e.g., CBT and contemporary variants such as ACT) and particularly unified approaches can be utilized in the development of interventions that can directly consider evidence of causal mechanisms of MNA, and address barriers while capitalizing on facilitators to MA. Modern technologies can also be harnessed, co-developed with patients and with quality-assurance methods employed, to ensure that the digital interventions are systematically evaluated and ensure patient-safety [47, 53]. Findings from this review can be easily translated into policymaking actions and interventions.

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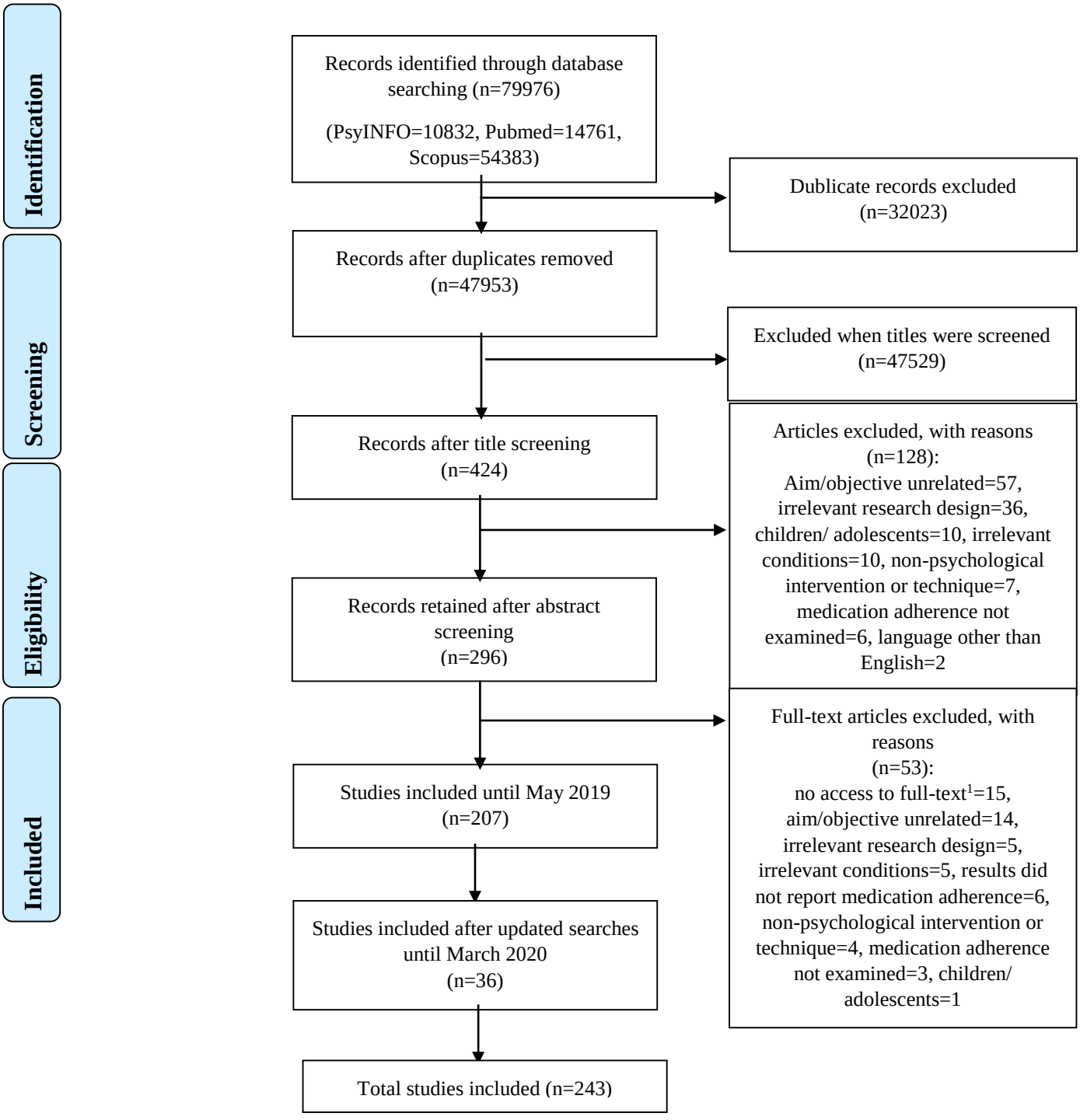
Figures


Identification
Screening
Eligibility
Included
Records identified through database searching (n=79976)
(PsyINFO=10832, Pubmed=14761, Scopus=54383)
Dublicate records excluded (n=32023)
Records after duplicates removed (n=47953)
Excluded when titles were screened (n=47529)
Records after title screening (n=424)
Articles excluded, with reasons (n=128): Aim/objective unrelated=57, irrelevant research design=36, children/ adolescents=10, irrelevant conditions=10, non-psychological intervention or technique=7, medication adherence not examined=6, language other than English=2
Records retained after abstract screening (n=296)
Full-text articles excluded, with reasons (n=53): no access to full-text[1]=15, aim/objective unrelated=14, irrelevant research design=5, irrelevant conditions=5, results did not report medication adherence=6, non-psychological intervention or technique=4, medication adherence not examined=3, children/ adolescents=1
Studies included until May 2019 (n=207)
Studies included after updated searches until March 2020 (n=36)
Total studies included (n=243)

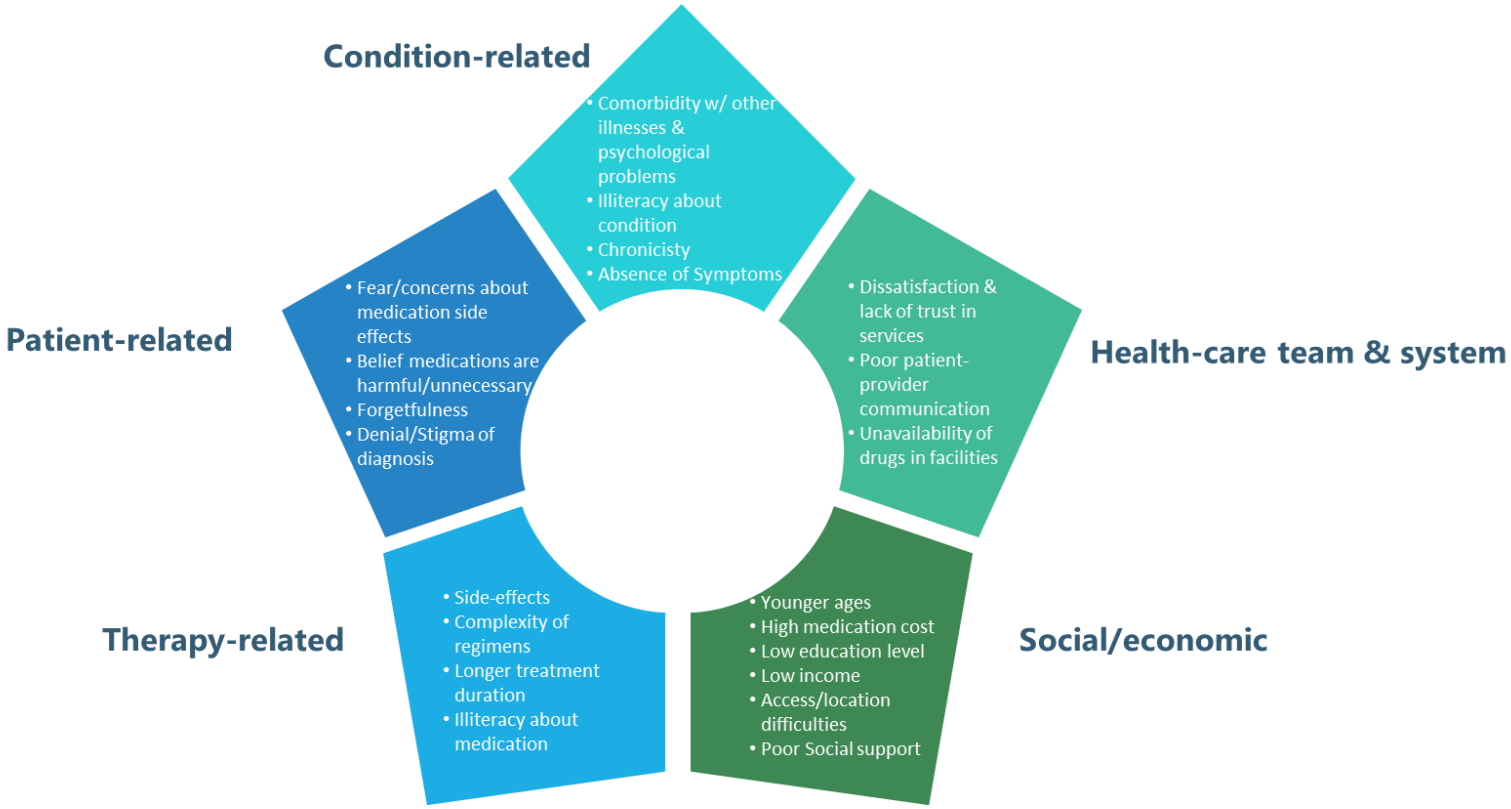

Condition-related
• Comorbidity w/ other illnesses & psychological problems
• Illiteracy about condition
• Chronicisty
• Absence of Symptoms
Patient-related
• Fear/concerns about medication side effects
• Belief medications are harmful/unnecessary
• Forgetfulness
• Denial/Stigma of diagnosis
Health-care team & system
• Dissatisfaction & lack of trust in services
• Poor patient-provider communication
• Unavailability of drugs in facilities
Therapy-related
• Side-effects
• Complexity of regimens
• Longer treatment duration
• Illiteracy about medication
Social/economic
• Younger ages
• High medication cost
• Low education level
• Low income
• Access/location difficulties
• Poor Social support

Figure Captions

Figure 1. Flow diagram of information from identification to inclusion of studies in this review.

Note. [1]An attempt was made to get the full-text by conducting the corresponding author of the article, but failed.

Figure 2. Most commonly reported medication adherence barriers across chronic conditions based on the WHO taxonomy (2003).

Appendices

Appendix A

Table 1

Authors (Date)	Setting (Health Care or Clinical Trial)	%MNA
	Barriers of MA[1]	
Asthma (*n*=9)		
Brandstetter et al., (2017) [1]	Health care	81.0%
Foot et al. (2019) [2]	Health care	M=19.2
Janson et al. (2008) [3]	Health care	NR
Makhinova et al. (2020) [4]	Health care	25.0%
Sarker et al. (2020) [5]	Health care	68.8%
Scherman & Löwhagen (2003) [6]	Health care	95.6%
Smits et al. (2020) [7]	Health care	66.1%
Sofianou et al. (2013) [8]	Health care	57.0%
Ulrik et al. (2006) [9]	Health care	51.0%
Cancer (*n*=4)		
Atkins & Fallowfield (2006) [10]	Health care	55.0%
Neugut et al. (2016) [11]	Health care	15.6%
Spencer et al. (2019) [12]	Health care	NR
Tzeng et al. (2008) [13]	Clinical trial	51.0%
Diabetes & Hypertension (*n*=1)		
Khayyat et al. (2019) [14]	Health care	54.3%
Diabetes (*n*=34)		
Abate (2019) [15]	Health care	68.8%
Abdullah et al. (2019) [16]	Health care	44.8%
Abebe, Berhane & Worku (2014) [17]	Health care	45.9%
Aminde et al. (2019) [18]	Health care	54.4%
Atekha (2018) [19]	Health care	26.8%
Atinga, Yarney, & Gavu (2018) [20]	Health care	NR
Baghikar et al. (2019) [21]	Clinical trial	NR
Bailey et al. (2012) [22]	Health care	56.0%
Banuelos Mota et al. (2019) [23]	Health care	NR
Benrazavy & Khalooei (2019) [24]	Health care	35.4%
Dehdari & Dehdari (2019) [25]	Health care	NR
Farhat et al. (2019) [26]	Health care	17.3%
Gutierrez & Long (2011) [27]	Health care	NR
Horii et al. (2019) [28]	Health care	50.2%
Jaam et al. (2018a) [29]	Health care	73.0%
Jaam et al. (2018b) [30]	Health care	NR
Jeragh-Alhaddad et al. (2015) [31]	Health care	NR
Kang & Hur (2019) [32]	Health care	30.3%
Kretchy et al. (2020) [33]	Health care	66.5%
Mohd et al. (2016) [34]	Health care	64.6%
Nelson et al. (2018) [35]	Health care	7.0%

Nonogaki et al. (2019) [36]	Health care	50.7%
Odegard & Gray (2008) [37]	Clinical trial	47.0%
Park et al. (2010) [38]	Health care	15.7%
Peeters et al. (2015) [39]	Health care	NR
Pereira et al. (2019) [40]	Health care	NR
Peres et al. (2020) [41]	Health care	36.8%
Rezaei et al. (2019) [42]	Health care	NR
Rezaie, Laghousi, Alizadeh (2019) [43]	Health care	85.0%
Shams et al. (2016) [44]	Health care	37.7%
Shiyanbola & Nelson (2011) [45]	Health care	56.3%
Sweileh et al. (2014) [46]	Health care	42.7%
Tristan (2015) [47]	Health care	46.5%
Zioga et al. (2016) [48]	Health care	45.9%
Epilepsy (*n*=10)		
Chapman et al. (2014) [49]	Health care	36.7%
Egenasi et al. (2015) [50]	Health care	45.4%
Elsayed et al. (2019) [51]	Health care	35.4%
Fadaye-Vatan et al. (2017) [52]	Health care	21.8%
Getnet et al. (2016) [53]	Health care	37.8%
Gurumurthy, Chanda & Sarma (2017) [54]	Health care	27.7%
Hamedi-Shahraki et al. (2019) [55]	Health care	48.7%
Honnekeri et al. (2018) [56]	Health care	9.9%
Paschal, Rush, & Sadler (2014) [57]	Health care	66%
Shaaban, Ishak, & Ismail (2011) [58]	Health care	52.2%
HIV/AIDS (*n*=88)		
Abdulrahman et al. (2017) [59]	Clinical trial	64.5%
Achappa et al. (2013) [60]	Health care	36.3%
Amberbir et al. (2008) [61]	Health care	20.8%
Anyaike et al. (2019) [62]	Health care	10.2%
Balcha, Jeppsson, & Bekele (2011) [63]	Health care	NR
Barnett et al. (2013) [64]	Health care	NR
Beer & Skarbinski (2014) [65]	Health care	40.0%
Bezabhe et al. (2014) [66]	Health care	NR
Boretzki et al. (2017) [67]	Health care	8.0%
Buscher et al. (2012) [68]	Health care	2.2%
Chime et al. (2019) [69]	Health care	10.5%
Curioso et a. (2010) [70]	Health care	NR
Do et al. (2010) [71]	Health care	18.7%
Dworkin et al. (2016) [72]	Health care	20.0%
Dyrehave et al. (2016) [73]	Health care	24.9%
Edwards (2006) [74]	Health care	NR
Ferguson et al. (2002) [75]	Health care	65.2%
Gauchet, Tarquinio, & Fischer (2007) [76]	Health care	NR
Gianotti et al. (2013) [77]	Health care	80.0%
Gordillo et al. (1999) [78]	Health care	42.4%
Grierson et al. (2011) [79]	Health care	39.1%
Gust et al. (2011) [80]	Health care	22.0%
Harris et al. (2011) [81]	Clinical trial	24.0%

Holstad et al. (2006) [82]	Health care	75.1%
Holtzman et al. (2015) [83]	Health care	NR
Holzemer et al. (1999) [84]	Health care	1.6%
Kalichman, Kalichman, & Cherry (2016) [85]	Health care	37.1%
Khalili et al. (2012) [86]	Health care	29.0%
Kioko, & Pertet (2017) [87]	Health care	NR
Konkle-Parker, Erlen, & Dubbert (2008) [88]	Health care	M=1.89
Kremer, Ironson, & Porr (2009) [89]	Health care	16.2%
Krummenacher et al. (2014) [90]	Health care	NR
Kumarasamy et al. (2005) [91]	Health care	28.2%
Legesse & Reta (2019) [92]	Health care	15.0%
Letta et al. (2015) [93]	Health care	58.3%
Leyva-Moral et al. (2019) [94]	Health care	3.1%
Li et al. (2014) [95]	Health care	34.5%
Maneesriwongul et al. (2006) [96]	Health care	5.0%
Masa, Chowa, & Nyirenda (2017) [97]	Clinical trial	33.0%
Mizuno et al. (2017) [98]	Health care	44.0%
Mo & Mak (2009) [99]	Health care	73.5%
Mukui et al. (2016) [100]	Health care	9.4%
Murphy et al. (2000) [101]	Health care	8.0%
Murray et al. (2009) [102]	Health care	NR
Muya et al. (2015) [103]	Health care	19.0%
Nakimuli-Mpungu et al. (2009) [104]	Health care	NR
Ncama et al. (2008) [105]	Clinical trial	21.0%
Nduaguba et al. (2017) [106]	Health care	20.5%
Negash & Ehlers (2013) [107]	Health care	26.5%
Negash et al. (2016) [108]	Health care	10.7%
Neupane, Dhungana, & Ghimire (2019) [109]	Health care	12.6%
O'Neil et al. (2012) [110]	Health care	44.2%
Odili et al. (2017) [111]	Health care	11.0%
Oh et al. (2009) [112]	Health care	68.5%
Oku et al. (2014) [113]	Health care	49.6%
Olowookere et al. (2007) [114]	Health care	37.1%
Pahari et al. (2015) [115]	Health care	23.0%
Patel et al. (2012) [116]	Health care	NR
Pellowski & Kalichman (2016) [117]	Clinical trial	16.5%
Penedo et al. (2003) [118]	Health care	28.0%
Phuphanich et al. (2016) [119]	Health care	NR
Pinheiro et al. (2002) [120]	Health care	43.1%
Pomeroy et al. (2007) [121]	Health care	29.0%
Portelli et al. (2015) [122]	Health care	NR
Rasmussen et al. (2013) [123]	Health care	NR
Remien et al. (2003) [124]	Health care	NR
Royal et al. (2009) [125]	Health care	29.6%
Sabin et al. (2008) [126]	Health care	NR
Sangeda et al. (2018) [127]	Health care	28.3%
Sanjobo, Frich, & Fretheim (2008) [128]	Health care	NR
Sarna et al. (2008) [129]	Health care	6.6%

Schneider et al. (2004) [130]	Health care	13.0%
Schönnesson et al. (2007) [131]	Health care	NR
Semvua et al. (2017) [132]	Health care	42.0%
Shigdel et al. (2014) [133]	Health care	26.6%
Suleiman & Momo (2016) [134]	Clinical trial	16.0%
Sullivan et al. (2007) [135]	Health care	15.8%
Suryana, Suharsono, & Antara (2019) [136]	Health care	17.3%
Tessema et al. (2010) [137]	Health care	27.6%
Tiyou et al. (2010) [138]	Clinical trial	NR
Tyer-Viola et al. (2014) [139]	Health care	NR
Van Servellen, & Lombardi (2005) [140]	Health care	13.3%
Wang & Wu (2007) [141]	Health care	18.2%
Watt et al. (2010) [142]	Health care	5.90%
Wolf et al. (2007) [143]	Health care	52.5%
Wondiye et al. (2016) [144]	Health care	NR
Yathiraj et al. (2016) [145]	Health care	29.6%
Yu et al. (2018) [146]	Health care	14.5%
Hypertension (*n*=41)		
Al-Ramahi, (2015) [147]	Health care	54.2%
Amira & Okubadejo (2007) [148]	Health care	34.2%
Bae et al., (2016) [149]	Health care	54.4%
Barreto, Reiners, & Marcon (2014) [150]	Health care	42.7%
Boima et al., (2015) [151]	Health care	66.7%
Braverman & Dedier (2009) [152]	Clinical trial	28.4%
Choi et al. (2018) [153]	Health care	18.3%
de Terline et al. (2019) [154]	Health care	30.8%
Espeche et al. (2020) [155]	Health care	14.3%
Hassanein (2020) [156]	Health care	32.6%
Holt et al. (2013) [157]	Health care	28.1%
Jarab et al. (2018) [158]	Health care	81.0%
Jokisalo et al. (2002) [159]	Health care	27.0%
Karakurt & Kaşikçi (2012) [160]	Health care	57.9%
Khadoura et al. (2020) [161]	Health care	65.8%
Khan, Shah, & Hameed (2014) [162]	Health care	21.0%
Kretchy et al. (2013) [163]	Health care	93.3%
Lee et al. (2013) [164]	Clinical trial	21.6%
Lehane & McCarthy (2007) [165]	Health care	NR
Lewis, Schoenthaler & Ogedegbe (2012) [166]	Clinical trial	54.9%
Li et al. (2012) [167]	Health care	47.5%
Lowry et al. (2005) [168]	Clinical trial	40.0%
Lulebo et al. (2015) [169]	Health care	54.2%
Mamaghani et al. (2020) [170]	Health care	18.2%
Martin et al. (2010) [171]	Clinical trial	60.1%
McLane, Zyzanski, & Flocke (1995) [172]	Health care	24.0%
Náfrádi et al. (2016) [173]	Health care	53.0%
Nair et al. (2011) [174]	Health care	39.0%
Najimi et al. (2018) [175]	Health care	NR
Ogedegbe et al. (2004) [176]	Health care	NR

Oluwole et al. (2019) [177]	Health care	9.8%
Palanisamy & Sumathy (2009) [178]	Health care	51.2%
Park et al. (2008) [179]	Health care	17.9%
Rajpura & Nayak (2014a) [180]	Health care	34.2%
Rajpura & Nayak (2014b) [181]	Health care	66.1%
Rimando (2013) [182]	Health care	NR
Ruppar, Dobbels, & De Geest (2012) [183]	Health care	48.5%
Saounatsou et al. (2001) [184]	Health care	NR
Stavropoulou (2012) [185]	Health care	26.0%
Tsiantou et al. (2010) [186]	Health care	NR
Vawter et al. (2008) [187]	Clinical trial	54.1%
Interventions used to help with MA[1]		
Asthma (*n*=4)		
MacDonell et al. (2016) [188]	Clinical trial	NR
Mohan et al. (2018) [189]	Clinical trial	74.0%
Strandbygaard et al. (2010) [190]	Clinical trial	22.1%
Weinstein et al. (2019) [191]	Clinical trial	11.3%
Cancer (*n*=2)		
Spoelstra et al. (2015) [192]	Clinical trial	27.0%
Spoelstra et al. (2016) [193]	Clinical trial	34.0%
Diabetes (*n*=12)		
Arora et al. (2014) [194]	Clinical trial	NR
Brath et al. (2013) [195]	Health care	NR
Gatwood et al. (2016) [196]	Clinical trial	16.6%
George et al. (2018) [197]	Health care	63.2%
	Clinical trial	IG: 28.6
Huang et al. (2019) [198]		CG: 27.2
Kjos, Vaughan, & Bhargava (2019) [199]	Health care	NR
	Clinical trial	IG: M=3.1
Li et al. (2020) [200]		CG: M=3.0
Melko et al. (2010) [201]	Health care	NR
Nelson et al., (2016) [202]	Health care	15.6%
	Clinical trial	IG: M=6.9
Owolabi et al. (2020) [203]		CG: M=6.9
Sugita et al. (2017) [204]	Clinical trial	NR
Vervloet et al. (2012) [205]	Clinical trial	NR
HIV/AIDS (*n*=26)		
Claborn (2013) [206]	Clinical trial	26.0%
Da Costa et al. (2012) [207]	Clinical trial	19.9%
Dilorio et al. (2008) [208]	Clinical trial	20.0%
Goujard et al. (2003) [209]	Clinical trial	NR
Guo et al. (2018) [210]	Clinical trial	16.0%
Haberer et al. (2016) [211]	Clinical trial	17.0%
Hardy et al. (2011) [212]	Clinical trial	28.3%
Hersch et al. (2013) [213]	Clinical trial	NR
Holstad et al. (2011) [214]	Clinical trial	25.8%
Johnson et al. (2007) [215]	Clinical trial	42.0%

Kalichman et al. (2016) [216]	Clinical trial	82.0%
Konkle-Parker et al. (2014) [217]	Clinical trial	65.0%
Levin et al. (2006) [218]	Clinical trial	2.9%
Mao et al. (2018) [219]	Clinical trial	17.7%
Murphy et al. (2002) [220]	Clinical trial	34.5%
Murphy et al. (2007) [221]	Clinical trial	27.5%
Nsagha et al. (2016) [222]	Clinical trial	42.2%
Pagan-Ortiz et al. (2019) [223]	Clinical trial	62.0%
Pop-Eleches et al. (2011) [224]	Clinical trial	53.5%
Rodrigues et al. (2012) [225]	Clinical trial	15.0%
Ruan et al. (2017) [226]	Clinical trial	18.2%
Safren et al. (2001) [227]	Clinical trial	7.5%
Scharer et al. (2019) [228]	Clinical trial	58.8%
Swendeman et al. (2015) [229]	Clinical trial	39.0%
Watakakosol (2010) [230]	Clinical trial	2.8%
Znoj et al. (2010) [231]	Clinical trial	55.3%
Hypertension (*n*=12)		
Costa et al. (2005) [232]	Clinical trial	4.2%
Davidson et al., (2015) [233]	Clinical trial	NR
Hacihasanoğlu & Gözüm (2011) [234]	Clinical trial	NR
Hamet et al. (2003) [235]	Clinical trial	NR
Márquez Contreras et al. (2019) [236]	Health care	25.7%
Maslakpak & Safaie (2016) [237]	Clinical trial	NR
Mirniam et al. (2019) [238]	Clinical trial	IG: M=3.86 CG: M=3.75
Patel et al. (2013) [239]	Health care	79.0%
Petry et al. (2015) [240]	Health care	NR
Ruppar (2009) [241]	Clinical trial	M=43.1%
Sheilini et al. (2019) [242]	Clinical trial	IG: M=5.59 CG: M=5.93
Varleta et al. (2017) [243]	Clinical trial	28.4%

Percentages of Medication Adherence (MA) Across Studies based on Setting (n=243)

Note. NR= Not Reported.
[1]Studies are listed alphabetically based on condition and then by the names of the authors.

Appendix B

a) Search strategy PsycInfo

(1) TI medication adherence OR TI medication intake OR TI medication concordance OR TI medication compliance

(2) AB medication adherence OR AB medication intake OR AB medication concordance OR AB medication compliance

b) Search strategy Pubmed

(1) (((medication adherence[Title/Abstract]) OR medication intake[Title/Abstract]) OR medication concordance[Title/Abstract]) OR medication compliance[Title/Abstract]

c) Search strategy Scopus

(1) (TITLE (medication AND adherence) OR TITLE (medication AND concordance) OR TITLE (medication AND intake) OR TITLE (medication AND compliance))

(2) (ABS (medication AND adherence) OR ABS (medication AND concordance) OR ABS (medication AND intake) OR ABS (medication AND compliance))

Note. TI= Title; AB= Abstract; ABS= Abstract

Appendix C

Information extracted by each study

1) Characteristics of the study: year of publication, location, research design, purpose of measuring MA (i.e., clinical trial: experiments or observations designed to answer specific questions about an intervention vs. health care/routine care: regular care that patients got from their doctors/physicians);

2) Characteristics of the population: type of chronic condition, sample size, age, gender;

3) Characteristics of MA: specific medication, definition of MA, and assessment method;

4) Barriers and facilitators: socioeconomic-related factors, health-care team and system factors, condition-related, therapy-related, and patient-related factors;

5) Type (i.e., digital, face-to-face, combination), length of interventions and description of intervention and control groups (where possible) were coded.

Appendix D

Characteristics of Included Studies (N = 243)

Authors (Date)	Country	Type of Study[2]	Research Design	Sample Size	Age[3] *(M, SD)*	Gender *(n, % females)*	Medication[5]
			Barriers of MA[1]				
Asthma (*n*=9)							
Brandstetter et al., (2017) [1]	Germany	Health care	Prospective[4]	402	56.7 (15.9)	20 (49.5)	PM
Foot et al. (2019) [2]	Australia	Health care	Cross-sectional	198	39.8 (12.7)	161 (81.7)	ICS
Janson et al. (2008) [3]	Sweden	Health care	Cross-sectional	30	33.0 (NR)	14 (46.7)	PM
Makhinova et al. (2020) [4]	USA	Health care	Cross-sectional[4]	267	47.0 (8.0)	183 (68.5)	ICS, IBA
Sarker et al. (2020) [5]	USA	Health care	Cross-sectional	49	45.4(17.2)	32 (65.3)	Inhalers
Scherman & Löwhagen (2003) [6]	Bangladesh	Health care	Cross-sectional	136	40-59: 69.9%	41 (30.0)	Inhalers
Smits et al. (2020) [7]	Latvia	Health care	Cross-sectional	352	57.5 (16.9)	264 (75.0)	Glucocorticoids
Sofianou et al. (2013) [8]	USA	Health care	Prospective[4]	242	67.4 (6.8)	203 (83.9)	ICS
Ulrik et al. (2006) [9]	Denmark	Health care	Cross-sectional	509	26–35: 48.0%	317 (62.0)	ASM
Cancer (*n*=4)							
Atkins & Fallowfield (2006) [10]	UK	Health care	Cross-sectional	131	59.4 (11.5)	131 (100)	HD
Neugut et al. (2016) [11]	USA	Health care	Retrospective	21255	55-64: 32.9%	21255 (100)	HD
Spencer et al. (2019) [12]	USA	Health care	Cross-sectional	1231	53.2 (10.9)	231(100)	ET
Tzeng et al. (2008) [13]	Taiwan	Clinical trial	Cross-sectional	135	58.4 (15.6)	80 (59.0)	Analgesics
Diabetes & Hypertension (*n*=1)							
Khayyat et al. (2019) [14]	S. Arabia	Health care	Cross-sectional	300	56.8 (12.8)	192 (64.0)	DM, AM
Diabetes (*n*=34)							
Abate (2019) [15]	Ethiopia	Health care	Cross-sectional	416	45.4 (16.7)	174 (41.8)	DM
Abdullah et al. (2019) [16]	Malaysia	Health care	Cross-sectional	232	56.7 (13.4)	124 (53.4)	ODM, insulin
Abebe, Berhane & Worku (2014) [17]	Ethiopia	Health care	Cross-sectional	407	50.4 (15.2)	207 (50.9)	DM
Aminde et al. (2019) [18]	Australia	Health care	Cross-sectional	195	60.5 (13.6)	136 (70.3)	DM
Atekha (2018) [19]	USA	Health care	Cross-sectional	56	50.1 (NR)	20 (35.7)	DM
Atinga, Yarney, & Gavu (2018) [20]	Africa	Health care	Cross-sectional	49	42.0 (37.5)	21 (42.9)	DM
Baghikar et al. (2019) [21]	USA	Clinical trial	Cross-sectional[4]	27	57.0 (11.0)	22 (81.0)	DM
Bailey et al. (2012) [22]	USA	Health care	Cross-sectional	59	50.4 (10.3)	25 (43.1)	DM
Banuelos Mota et al. (2019) [23]	USA	Health care	Cross-sectional	120	60.0 (12.0)	74 (62.0)	DM
Benrazavy & Khalooei (2019) [24]	Iran	Health care	Cross-sectional	589	56.4 (12.0)	400 (67.9)	DM
Dehdari & Dehdari (2019) [25]	Iran	Health care	Qualitative	22	56.7 (9.2)	12 (54.5)	DM
Farhat et al. (2019) [26]	Lebanon	Health care	Cross-sectional	214	53.2 (9.2)	99 (46.3)	ODM
Gutierrez & Long (2011) [27]	USA	Health care	Prospective	152	57.7 (6.9)	29 (19.0)	DM
Horii et al. (2019) [28]	Japan	Health care	Retrospective	884	47.0 (8.1)	87 (9.8)	OHA
Jaam et al. (2018a) [29]	Qatar	Health care	Cross-sectional	260	56.1 (10.4)	115 (44.2)	DM

Jaam et al. (2018b) [30]	Qatar	Health care	Retrospective	14	58.3 (8.1)	4 (28.6)	DM
Jeragh-Alhaddad et al. (2015) [31]	Kuwait	Health care	Cross-sectional	20	53.7 (NR)	10 (50.0)	DM
Kang & Hur (2019) [32]	Korea	Health care	Cross-sectional	175	56.6 (11.2)	118 (67.4)	DM
Kretchy et al. (2020) [33]	Africa	Health care	Cross-sectional	188	59.3 (11.9)	136 (72.3)	DM
Mohd et al. (2016) [34]	Dubai	Health care	Cross-sectional	446	61.0 (11.0)	230 (51.6)	DM
Nelson et al. (2018) [35]	USA	Health care	Cross-sectional	237	54.7 (9.8)	126 (53.0)	DM
Nonogaki et al. (2019) [36]	Africa	Health care	Cross-sectional	773	55-64: 38.4%	445 (57.6)	ODM
Odegard & Gray (2008) [37]	USA	Clinical trial	Cross-sectional[4]	77	52 (10.9)	34 (44.2)	ODM
Park et al. (2010) [38]	Korea	Health care	Cross-sectional	262	70-74: 36.6%	162 (61.8)	DM
Peeters et al. (2015) [39]	Belgium	Health care	Retrospective	21	40–49: 33.3%	12 (57.1)	ODM
Pereira et al. (2019) [40]	Portugal	Health care	Cross-sectional	387	59.2 (NR)	162 (41.9)	ODM
Peres et al. (2020) [41]	Brazilia	Health care	Cross-sectional	158	58.0 (15.5)	73 (46.0)	DM
Rezaei et al. (2019) [42]	Iran	Health care	Qualitative	12	52.3 (10.2)	7 (58.3)	Insulin, glucose
Rezaie, Laghousi, Alizadeh (2019) [43]	Iran	Health care	Cross-sectional	320	58.1 (13.7)	204 (63.8)	DM
Shams et al. (2016) [44]	Pakistan	Health care	Cross-sectional	183	56.6 (10.6)	140 (76.5)	DM
Shiyanbola & Nelson (2011) [45]	USA	Health care	Cross-sectional	16	46.1 (10.2)	16 (100)	DM
Sweileh et al. (2014) [46]	Palestine	Health care	Cross-sectional	405	58.3 (10.4)	216 (53.3)	DM
Tristan (2015) [47]	USA	Health care	Retrospective	200	46-60: 92 (46.0)	140 (70.0)	DM
Zioga et al. (2016) [48]	Greece	Health care	Cross-sectional	108	66.7 (10.9)	57 (57.8)	DM
Epilepsy (*n*=10)							
Chapman et al. (2014) [49]	UK	Health care	Cross-sectional	398	49.9 (16.4)	215 (54.6)	AED
Egenasi et al. (2015) [50]	Africa	Health care	Prospective	197	39.9 (NR)	75 (38.1)	AED
Elsayed et al. (2019) [51]	Africa	Health care	Cross-sectional	96	29.0 (12.8)	64 (67.0)	AED
Fadaye-Vatan et al. (2017) [52]	Iran	Health care	Cross-sectional	23	63.3 (3.3)	6 (26.0)	AED
Getnet et al. (2016) [53]	Ethiopia	Health care	Cross-sectional	450	MDN: 27.0 (NR)	186 (41.3)	AED
Gurumurthy, Chanda & Sarma (2017) [54]	India	Health care	Cross-sectional	451	27.3 (8.1)	200 (44.3)	AED
Hamedi-Shahraki et al. (2019) [55]	Iran	Health care	Prospective	766	73.9 (5.7)	419 (54.7)	AED
Honnekeri et al. (2018) [56]	India	Health care	Cross-sectional	313	37.4 (14.1)	NR	AED
Paschal, Rush, & Sadler (2014) [57]	USA	Health care	Cross-sectional	180	25-46: 53.0%	91 (57.0)	AED
Shaaban, Ishak, & Ismail (2011) [58]	Malaysia	Health care	Cross-sectional	297	31.7 (11.1)	160 (53.9)	OAD
HIV/AIDS (*n*=88)							
Abdulrahman et al. (2017) [59]	Malaysia	Clinical trial	Cross-sectional	242	33.4 (9.2)	27 (11.2)	ART
Achappa et al. (2013) [60]	India	Health care	Cross-sectional	116	NR	36 (31.0)	ART
Amberbir et al. (2008) [61]	Ethiopia	Health care	Prospective	400	MDN: 30.0 (NR)	239 (59.8)	ART
Anyaike et al. (2019) [62]	Nigeria	Health care	Cross-sectional	550	39.9 (10.0)	329 (59.8)	cART
Balcha, Jeppsson, & Bekele (2011) [63]	Ethiopia	Health care	Cross-sectional	14	NR	9 (64.0)	ART
Barnett et al. (2013) [64]	Africa	Health care	Cross-sectional	10	NR	9 (90.0)	ART
Beer & Skarbinski (2014) [65]	USA	Health care	Cross-sectional	3606	NR	914 (26.0)	ART
Bezabhe et al. (2014) [66]	Ethiopia	Health care	Cross-sectional	24	36.0 (NR)	12 (50.0)	ART

Boretzki et al. (2017) [67]	Germany	Health care	Cross-sectional	215	MDN: 47.0 (NR)	43 (20.0)	ART
Buscher et al. (2012) [68]	USA	Health care	Prospective	99	30-39: 35.4%	27 (27.3)	ART
Chime et al. (2019) [69]	Nigeria	Health care	Retrospective	840	38.5 (9.8)	641 (76.3)	ART
Curioso et a. (2010) [70]	Peru	Health care	Cross-sectional	31	NR	3 (10.0)	ART
Do et al. (2010) [71]	Africa	Health care	Cross-sectional	300	30-35: 32.7%	229 (76.3)	ART
Dworkin et al. (2016) [72]	India	Health care	Cross-sectional	211	MDN: 34.0	97 (46.0)	ART
Dyrehave et al. (2016) [73]	Africa	Health care	Cross-sectional	494	26-44: 63.2%	369 (75.0)	ART
Edwards (2006) [74]	USA	Health care	Cross-sectional	20	39.0 (NR)	20 (100)	ART
Ferguson et al. (2002) [75]	USA	Health care	Cross-sectional	149	39.0 (8.6)	19 (12.8)	ART
Gauchet, Tarquinio, & Fischer (2007) [76]	France	Health care	Cross-sectional	127	39.7 (9.2)	28 (22.0)	ART
Gianotti et al. (2013) [77]	Italy	Health care	Cross-sectional	2114	46.9 (8.8)	449 (21.2)	ART
Gordillo et al. (1999) [78]	Spain	Health care	Cross-sectional	366	MDN: 35.0	87 (23.7)	ART
Grierson et al. (2011) [79]	Australia	Health care	Cross-sectional	1106	NR	NR	ART
Gust et al. (2011) [80]	Botswana	Health care	Retrospective	379	35.5 (8.5)	285 (75.2)	ART
Harris et al. (2011) [81]	Dominican Rep.	Clinical trial	Cross-sectional	300	<35: 50.0% (NR)	165 (53.3)	ART
Holstad et al. (2006) [82]	USA	Health care	Cross-sectional	120	36.5 (8.5)	42 (35.0)	ART
Holtzman et al. (2015) [83]	USA	Health care	Cross-sectional	51	MDN: 45.0	24 (47.0)	ART
Holzemer et al. (1999) [84]	USA	Health care	Cross-sectional	420	39.4 (7.4)	84 (20.0)	ART
Kalichman, Kalichman, & Cherry (2016) [85]	USA	Health care	Prospective	942	45.4 (9.6)	265 (28.1)	ART
Khalili et al. (2012) [86]	Iran	Health care	Cross-sectional	73	35.1 (8.5)	20 (27.4)	ART
Kioko, & Pertet (2017) [87]	Kenya	Health care	Cross-sectional	301	40.4 (10.8)	189 (62.7)	ART
Konkle-Parker, Erlen, & Dubbert (2008) [88]	USA	Health care	Cross-sectional	20	NR	8 (40.0)	ART
Kremer, Ironson, & Porr (2009) [89]	USA	Health care	Cross-sectional	79	42.0 (7.9)	28 (35.0)	ART
Krummenacher et al. (2014) [90]	Switzerland	Health care	Retrospective	17	40-49: 41.2%	8 (47.1)	ART
Kumarasamy et al. (2005) [91]	India	Health care	Cross-sectional	60	≤30: 30.3%	11 (18.3)	ART
Legesse & Reta (2019) [92]	Ethiopia	Health care	Cross-sectional	418	38.2 (NR)	246 (58.9)	ART
Letta et al. (2015) [93]	Ethiopia	Health care	Cross-sectional	626	36.7 (10.7)	307 (49.5)	ART
Leyva-Moral et al. (2019) [94]	Peru	Health care	Cross-sectional	180	MDN: 30.0 (NR)	36 (20.0)	ART
Li et al. (2014) [95]	Thailand	Health care	Cross-sectional	128	45.0 (NR)	76 (59.4)	ART
Maneesriwongul et al. (2006) [96]	Thailand	Health care	Cross-sectional	149	MDN: 36.0 (NR)	71 (48.0)	ART
Masa, Chowa, & Nyirenda (2017) [97]	Africa	Clinical trial	Cross-sectional	101	38.0 (NR)	57 (56.0)	ART
Mizuno et al. (2017) [98]	USA	Health care	Cross-sectional		43.3 (NR)	258 (100)	ART
Mo & Mak (2009) [99]	Hong Kong	Health care	Cross-sectional	102	41.9 (10.0)	13 (12.7)	ART
Mukui et al. (2016) [100]	Africa	Health care	Cross-sectional	186	Age 30+: 86.6%	141 (75.8)	ART
Murphy et al. (2000) [101]	USA	Health care	Cross-sectional	39	NR	12 (31.0)	ART
Murray et al. (2009) [102]	Africa	Health care	Prospective	33	NR	33 (100)	ART
Muya et al. (2015) [103]	Tanzania	Health care	Prospective	44204	37.7 (9.6)	30501 (69.0)	ART

Nakimuli-Mpungu et al. (2009) [104]	Africa	Health care	Cross-sectional	122	36 (8.2)	96 (78.7)	ART
Ncama et al. (2008) [105]	Africa	Clinical trial	Cross-sectional	149	35.5 (7.5)	95 (64.0)	ART
Nduaguba et al. (2017) [106]	Nigeria	Health care	Cross-sectional	361	31-40: 42.7%	210 (58.3)	ART
Negash & Ehlers (2013) [107]	Ethiopia	Health care	Cross-sectional	383	33.1 (7.8)	229 (59.8)	ART
Negash et al. (2016) [108]	Ethiopia	Health care	Cross-sectional	355	36.4 (NR)	225 (63.4)	ART
Neupane, Dhungana, & Ghimire (2019) [109]	Nepal	Health care	Cross-sectional	231	38.6 (6.8)	134 (58.0)	ART
O'Neil et al. (2012) [110]	Canada	Health care	Cross-sectional	566	MDN: 40 (NR)	151 (26.7)	ART
Odili et al. (2017) [111]	Nigeria	Health care	Prospective	300	35.0 (8.7)	215 (71.7)	ART
Oh et al. (2009) [112]	USA	Health care	Prospective	1102	NR	0 (0)	ART
Oku et al. (2014) [113]	Nigeria	Health care	Cross-sectional	393	35.9 (9.6)	318 (80.9)	ART
Olowookere et al. (2007) [114]	Nigeria	Health care	Cross-sectional	318	39.1 (9.6)	173 (54.4)	ART
Pahari et al. (2015) [115]	India	Health care	Cross-sectional	128	31-40: 53%	82 (64.0)	ART
Patel et al. (2012) [116]	India	Health care	Cross-sectional	30	NR	NR	ART
Pellowski & Kalichman (2016) [117]	USA	Clinical trial	Cross-sectional	437	46.5 (7.8)	135 (30.9)	ART
Penedo et al. (2003) [118]	USA	Health care	Cross-sectional	116	39.2 (8.7)	52 (45.0)	ART
Phuphanich et al. (2016) [119]	Thailand	Health care	Cross-sectional	21	MDN: 43	9 (43.0)	ART
Pinheiro et al. (2002) [120]	Brazil	Health care	Cross-sectional	195	35 (NR)	76 (39.0)	ART
Pomeroy et al. (2007) [121]	USA	Health care	Cross-sectional	184	43.2 (7.3)	28 (15.0)	ART
Portelli et al. (2015) [122]	Asia	Health care	Cross-sectional	43	31-40: 39.5%	18 (41.9)	ART
Rasmussen et al. (2013) [123]	Africa	Health care	Cross-sectional	20	MDN: 38.5% (NR)	11 (55.0)	ART
Remien et al. (2003) [124]	USA	Health care	Cross-sectional	110	40.2 (7.0)	40 (36.4)	ART
Royal et al. (2009) [125]	USA	Health care	Cross-sectional	358	42.0 (NR)	100 (28.0)	ART
Sabin et al. (2008) [126]	China	Health care	Cross-sectional	36	26-30: 30.6%	17 (47.2)	ART
Sangeda et al. (2018) [127]	Tanzania	Health care	Prospective	220	MDN: 39.0 (NR)	140 (63.6)	ART
Sanjobo, Frich, & Fretheim (2008) [128]	Africa	Health care	Cross-sectional	60	30-39: 55.0%	27 (45.0)	ART
Sarna et al. (2008) [129]	India	Health care	Cross-sectional	310	MDN: 36.0 (NR)	49 (16.0)	ART
Schneider et al. (2004) [130]	USA	Health care	Cross-sectional	554	41.6 (7.7)	84 (15.2)	ART
Schönnesson et al. (2007) [131]	Sweden	Health care	Cross-sectional	193	34-43: 43.0%	48 (25.0)	ART
Semvua et al. (2017) [132]	Tanzania	Health care	Cross-sectional	228	44.0 (11.0)	151 (66.2)	ART
Shigdel et al. (2014) [133]	Nigeria	Health care	Cross-sectional	601	26-35: 52.2%	348 (57.9)	ART
Suleiman & Momo (2016) [134]	USA	Clinical trial	Cross-sectional	8908	40+: 51.0%	2487 (28.0)	ART
Sullivan et al. (2007) [135]	Indonesia	Health care	Cross-sectional	202	35+: 50.5%	79 (39.1)	ART
Suryana, Suharsono, & Antara (2019) [136]	Ethiopia	Health care	Cross-sectional	504	35.3 (8.9)	310 (61.5)	ART
Tessema et al. (2010) [137]	Ethiopia	Health care	Cross-sectional	319	35.1 (7.7)	175 (54.9)	ART
Tiyou et al. (2010) [138]	USA	Clinical trial	Cross-sectional	338	45 (9.1)	338 (100)	ART
Tyer-Viola et al. (2014) [139]	USA	Health care	Cross-sectional	85	40.0 (8.9)	4 (10.0)	ART
Van Servellen, & Lombardi (2005) [140]	Nepal	Health care	Cross-sectional	316	35-49: 46.8%	112 (35.4)	ART

Wang & Wu (2007) [141]	China	Health care	Cross-sectional	181	47.8 (11.3)	108 (59.7)	ART
Watt et al. (2010) [142]	Tanzania	Health care	Cross-sectional	340	31-40: 47.1%	252 (74.1)	ART
Wolf et al. (2007) [143]	USA	Health care	Cross-sectional	204	40.1 (9.2)	41 (20.1)	ART
Wondiye et al. (2016) [144]	Ethiopia	Health care	Cross-sectional	23	≤35: 65.2%	13 (56.5)	ART
Yathiraj et al. (2016) [145]	India	Health care	Cross-sectional	409	40+: 59.9%	153 (37.4)	ART
Yu et al. (2018) [146]	China	Health care	Cross-sectional	207	35.0 (12.0)	23 (11.1)	ART
Hypertension (*n*=41)							
Al-Ramahi, (2015) [147]	Palestine	Health care	Cross-sectional	500	59.1 (12.2)	253 (56.2)	AM[6]
Amira & Okubadejo (2007) [148]	Nigeria	Health care	Cross-sectional	225	55.1 (12.4)	135 (60.0)	AM[6]
Bae et al., (2016) [149]	China	Health care	Cross-sectional	401	74.5 (NR)	303 (75.6)	AM[6]
Barreto, Reiners, & Marcon (2014) [150]	Brazil	Health care	Cross-sectional	422	>60: 62.8%	251 (59.5)	AM[6]
Boima et al., (2015) [151]	Africa	Health care	Cross-sectional	357	56.6 (13.2)	205 (57.4)	AM[6]
Braverman & Dedier (2009) [152]	USA	Clinical trial	Cross-sectional[4]	70	58 (11.0)	49 (70.0)	AM[6]
Choi et al. (2018) [153]	China	Health care	Prospective	1523	50–64: 43.2%	616 (40.5)	ARBs
de Terline et al. (2019) [154]	Africa	Health care	Cross-sectional	2198	58.3 (11.8)	1323 (60.2)	AM
Espeche et al. (2020) [155]	Argentina	Health care	Cross-sectional	1111	62.0 (12.0)	549 (49.4)	AM
Hassanein (2020) [156]	Egypt	Health care	Cross-sectional	2000	55.8(10.9)	960 (48.0)	AM
Holt et al. (2013) [157]	USA	Health care	Cross-sectional	2194	75.0 (5.5)	1283 (58.5)	AM[6]
Jarab et al. (2018) [158]	Jordan	Health care	Cross-sectional	300	58.7 (11.3)	154 (51.3)	AM[6]
Jokisalo et al. (2002) [159]	Finland	Health care	Cross-sectional	1561	64.2 (11.4)	946 (60.6)	AM[6]
Karakurt & Kaşikçi (2012) [160]	Turkey	Health care	Cross-sectional	750	60–69: 27.2%	585 (78.0)	AM[6]
Khadoura et al. (2020) [161]	Palestine	Health care	Cross-sectional	538	57.1 (NR)	328 (61.0)	AM
Khan, Shah, & Hameed (2014) [162]	UK	Health care	Cross-sectional	200	30-40: 43.3%	123 (61.5)	AM[6]
Kretchy et al. (2013) [163]	Africa	Health care	Cross-sectional	400	57.1 (10.9)	251 (62.8)	AM[6]
Lee et al. (2013) [164]	China	Clinical trial	Retrospective	78558	61.8 (13.6)	39515 (50.3)	AM[7]
Lehane & McCarthy (2007) [165]	Ireland	Health care	Cross-sectional	73	NR	31 (42.0)	AM[6]
Lewis, Schoenthaler & Ogedegbe (2012) [166]	USA	Clinical trial	Cross-sectional[4]	253	56.6 (11.6)	0 (0)	AM[6]
Li et al. (2012) [167]	China	Health care	Cross-sectional	200	60.4 (11.5)	76 (38)	AM[6]
Lowry et al. (2005) [168]	UK	Clinical trial	Cross-sectional[4]	588	63.4 (11.4)	10 (1.7)	AM[7]
Lulebo et al. (2015) [169]	Congo	Health care	Cross-sectional	395	63.3 (9.6)	300 (75.9)	AM[6]
Mamaghani et al. (2020) [170]	Iran	Health care	Cross-sectional	238	57.4 (15.5)	161 (67.6)	AM
Martin et al. (2010) [171]	UK	Clinical trial	Cross-sectional[4]	434	56.1 (13.1)	293 (67.5)	AM[6]
McLane, Zyzanski, & Flocke (1995) [172]	USA	Health care	Cross-sectional	62	73.0 (NR)	46 (74.0)	AM[6]
Náfrádi et al. (2016) [173]	Switzerland	Health care	Cross-sectional	109	63.3 (11.3)	40 (36.7)	AM[6]
Nair et al. (2011) [174]	USA	Health care	Cross-sectional	8692	63.4 (13.7)	4282 (49.3)	AM[8]
Najimi et al. (2018) [175]	Iran	Health care	Cross-sectional	18	42.3 (9.8)	NR	AM[6]
Ogedegbe et al. (2004) [176]	USA	Health care	Cross-sectional	106	55.7 (12.8)	61 (58.0)	AM[6]

Oluwole et al. (2019) [177]	Nigeria	Health care	Cross-sectional	500	58.9 (13.3)	284 (56.8)	AM
Palanisamy & Sumathy (2009) [178]	India	Health care	Cross-sectional	120	59.6 (11.7)	43 (35.8)	AM[6]
Park et al. (2008) [179]	Korea	Health care	Cross-sectional	2455193	60–69: 31.6%	1426469 (80.7)	AM[6]
Rajpura & Nayak (2014a) [180]	USA	Health care	Cross-sectional	117	> 65: 52.1%	42 (35.9)	AM[6]
Rajpura & Nayak (2014b) [181]	USA	Health care	Cross-sectional	117	> 65: 52.1%	42 (35.9)	AM[6]
Rimando (2013) [182]	Georgia	Health care	Cross-sectional	28	62 (5.6)	22 (78.6)	AM[6]
Ruppar, Dobbels, & De Geest (2012) [183]	USA	Health care	Prospective	33	MDN: 74.0 (NR)	26 (79.0)	AM[6]
Saounatsou et al. (2001) [184]	Greece	Health care	RCT	40	IG: 60.5 (5.7) CG: 58.2 (5.8)	29 (72.5)	AM[6]
Stavropoulou (2012) [185]	Greece	Health care	Cross-sectional	743	61.0 (NR)	449 (60.0)	AM[6]
Tsiantou et al. (2010) [186]	Greece	Health care	Cross-sectional	43	IG: 63.7 (NR) CG: 44.6 (NR)	22 (51.2)	AM[6]
Vawter et al. (2008) [187]	USA	Health care	Cross-sectional	1432	≥65: 29.0%	774 (54.1)	AM[6]
			Interventions used to help with MA[1]				
Asthma (*n*=4)							
MacDonell et al. (2016) [188]	Canada	Clinical trial	RCT	48	22.4 (3.8)	36 (75.0)	ACM
Mohan et al. (2018) [189]	India	Clinical trial	Prospective	100	NR	55 (55.0)	ASM
Strandbygaard et al. (2010) [190]	Denmark	Clinical trial	RCT	26	32.2 (NR)	12 (46.2)	ICS/LABA/both
Weinstein et al. (2019) [191]	USA	Clinical trial	RCT	50	40.0 (NR)	27 (60.7)	ICS
Cancer (*n*=2)							
Spoelstra et al. (2015) [192]	USA	Clinical trial	RCT	80	58.5 (10.7)	48 (60.0)	OAs
Spoelstra et al. (2016) [193]	USA	Clinical trial	RCT	75	IG: 60.1 (10.1) CG: 59.9 (11.2)	39 (52.0)	OAs
Diabetes (*n*=12)							
Arora et al. (2014) [194]	USA	Clinical trial	RCT	128	50.7 (10.2)	82 (64.0)	DM
Brath et al. (2013) [195]	Austria	Health care	RCT	53	69.4 (4.8)	24 (45.3)	Various Med.[8]
Gatwood et al. (2016) [196]	USA	Clinical trial	RCT	48	IG: 47.5 (12.1) CG: 46.4 (11.6)	24 (50.0)	DM
George et al. (2018) [197]	India	Health care	Retrospective	98	50–59: 35.7%	37 (38.0)	DM
Huang et al. (2019) [198]	Singapore	Clinical trial	RCT	51	IG: 51.5 (NR) CG: 52.0 (NR)	21 (51.2)	ODM, insulin
Kjos, Vaughan, & Bhargava (2019) [199]	USA	Health care	Prospective	51	52.3 (10.2)	28 (54.9)	DM
Li et al. (2020) [200]	China	Clinical trial	RCT	225	59.6 (13.1)	111(49.3)	DM
Melko et al. (2010) [201]	USA	Health care	Prospective	27	51.0 (NR)	21 (78.0)	ODM
Nelson et al., (2016) [202]	USA	Health care	Non-RCT	240	IG: 50.1 (10.5) CG: 55.3 (12.3)	143 (59.6)	DM
Owolabi et al. (2020) [203]	Africa	Clinical trial	RCT	216	60.6 (11.6)	182 (87.5)	DM
Sugita et al. (2017) [204]	China	Clinical trial	RCT	41	IG: 55.6 (10.6)	12 (29.3)	Oral/Injectable

Vervloet et al. (2012) [205]	Netherlands	Clinical trial	RCT	104	CG: 56.3 (10.0) IG: 54.9 (6.6) CG: 54.6 (6.9)	47 (45.2)	DM
HIV/AIDS (*n*=26)							
Claborn (2013) [206]	USA	Clinical trial	RCT	97	44.0 (9.8)	16 (16.5)	HAART
Da Costa et al. (2012) [207]	Brazil	Clinical trial	RCT	21	34.6 (6.9)	21 (100)	ART
Dilorio et al. (2008) [208]	USA	Clinical trial	RCT	213	41 (7.1)	70 (33.0)	ART
Goujard et al. (2003) [209]	France	Clinical trial	RCT	326	40.5 (NR)	65 (20.0)	HAART
Guo et al. (2018) [210]	China	Clinical trial	RCT	62	28.3 (6.1)	6 (10.0)	ART
Haberer et al. (2016) [211]	Uganda	Clinical trial	RCT	62	MDN: 30 (NR)	40 (65.0)	ART
Hardy et al. (2011) [212]	USA	Clinical trial	RCT	19	42.7 (6.5)	9 (47.4)	ART
Hersch et al. (2013) [213]	USA	Clinical trial	RCT	168	46.0 (NR)	45 (27.0)	ART
Holstad et al. (2011) [214]	USA	Clinical trial	RCT	203	43.5 (9.2)	203 (100)	ART
Johnson et al. (2007) [215]	USA	Clinical trial	RCT	204	40.0 (6.3)	45 (22.1)	ART
Kalichman et al. (2016) [216]	USA	Clinical trial	RCT	600	IG: 47.4 (9.5) CG: 46.8 (9.5)	172 (28.7)	ART
Konkle-Parker et al. (2014) [217]	USA	Clinical trial	RCT	99	37.4 (9.0)	51 (51.0)	ART
Levin et al. (2006) [218]	USA	Clinical trial	RCT	59	IG MDN: 39.0 (NR) CG MDN: 43.0 (NR)	NR	HAART
Mao et al. (2018) [219]	Australia	Clinical trial	RCT	62	MDN: 51.5 (NR)	0 (0)	ART
Murphy et al. (2002) [220]	USA	Clinical trial	RCT	33	39.0 (6.9)	4.0 (12.0)	ART
Murphy et al. (2007) [221]	USA	Clinical trial	RCT	141	39.9 (7.1)	24.8 (17.6)	HAART
Nsagha et al. (2016) [222]	Africa	Clinical trial	RCT	90	38.8 (1.1)	55.0 (61.1)	ART
Pagan-Ortiz et al. (2019) [223]	USA	Clinical trial	Prospective	21	55.0 (5.4)	11.0 (52.4)	ART
Pop-Eleches et al. (2011) [224]	Africa	Clinical trial	RCT	431	IG: 36.5 (NR) CG: 35.7 (NR)	428 (59.4)	ART
Rodrigues et al. (2012) [225]	India	Clinical trial	Retrospective	150	38.54 (7.7)	41 (27.0)	ART
Ruan et al. (2017) [226]	China	Clinical trial	RCT	100	40.3 (9.8)	41 (41.0)	ART
Safren et al. (2001) [227]	USA	Clinical trial	RCT	140	IG: 40.8 (8.3) CG: 40.0 (8.5)	15 (10.7)	HAART
Scharer et al. (2019) [228]	USA	Clinical trial	RCT	34	47.1 (12.8)	13 (38.2)	ART
Swendeman et al. (2015) [229]	India	Clinical trial	RCT	46	36.0 (NR)	37 (80.4)	ART
Watakakosol (2010) [230]	USA	Clinical trial	RCT	42	52.1 (7.9)	17 (40.5)	ART
Znoj et al. (2010) [231]	Switzerland	Clinical trial	RCT	53	44.3 (10.7)	10 (18.9)	ART
Hypertension (*n*=12)							
Costa et al. (2005) [232]	Portugal	Clinical trial	RCT	71	58.0 (NR)	38 (53.0)	ACEI
Davidson et al., (2015) [233]	USA	Clinical trial	RCT	38	IG: 47.5 (11.8) CG: 48.5 (11.3)	23 (60.5)	AM[6]
Hacihasanoğlu & Gözüm (2011) [234]	Turkey	Clinical trial	RCT	120	56.9 (8.5)	62 (51.0)	AM[6]
Hamet et al. (2003) [235]	Canada	Clinical trial	RCT	4864	57.7 (NR)	2488 (51.0)	Irbesartan

Márquez Contreras et al. (2019) [236]	Spain	Health care	RCT	148	57.5 (9.9)	77 (52.0)	AM[6]
Maslakpak & Safaie (2016) [237]	Iran	Clinical trial	RCT	123	TM: 53.7 (6.9) RC: 50.3 (10.5) CG: 50.5 (8.1)	87 (70.7)	AM[6]
Mirniam et al. (2019) [238]	Iran	Clinical trial	RCT	72	IG: 59.2 (12.6) CG: 58.4 (12.6)	37 (59.7)	AM
Patel et al. (2013) [239]	USA	Health care	Prospective	50	53.0 (8.7)	35 (69.0)	AM[6]
Petry et al. (2015) [240]	USA	Health care	RCT	29	50.4 (11.0)	16 (55.2)	AM[6]
Ruppar (2009) [241]	USA	Clinical trial	RCT	15	72.5 (8.5)	11 (73.0)	AM[9]
Sheilini et al. (2019) [242]	India	Clinical trial	RCT	124	60-70: 68.6%	65 (52.4)	AM
Varleta et al. (2017) [243]	Chile	Clinical trial	RCT	314	IG: 60.7 (10.4) CG: 59.9 (10.7)	203 (64.6)	AM[6]

Note. CG= Control group; IG= Intervention Group; MA= Medication Adherence; NR= Not Reported; RCT= Randomized Controlled Trial.

[1]Studies are listed alphabetically based on condition and then by the names of the authors.

[2]Clinical trials are defined as experiments or observations designed to answer specific questions about interventions (e.g., evaluating new drugs).

[3]For studies not reporting mean age, frequencies with the highest percentage or median are presented instead, MDN= Median; TM= Text messaging; RC= Reminder cards; I= Interviews; FG= Focus Groups.

[4]The study was part of another study.

[5]ACEI= Angiotensin-converting enzyme inhibitor; ACM= asthma controller medication; AED= antiepileptic drug; AM= Antihypertensive medication; ASM= Asthma medication; DM= Diabetes medication; ET= Endocrine Therapy; HD= Hormonal drugs; IBA= inhaled beta-agonist; ICS= inhaled corticosteroids; LABA= long acting b2-agonist; OAD= oral antiepileptic drug; OAs= oral anticancer agents; ODM= oral diabetes medication; OHA= oral hypoglycaemic agents; PM= Prescribed medicine.

[6]The study reported that patients received generally an antihypertensive medication- and not the specific medication.

[7]Patient received at least one of the following antihypertensive drugs: diuretics, a-blockers, b-blockers, calcium, channel blockers (CCBs), angiotensin-converting, enzyme inhibitors (ACEIs), angiotensin receptor blockers, (ARBs) or other classes of antihypertensive drugs).

[8]Various medication included metformin (for diabetes), simvastatin and rosuvastatin (for hypercholesterolaemia condition) and ramipril (for hypertension).

[9]Antihypertensive medication included drug classes of alpha-blockers, beta-blockers, calcium channel blockers, diuretics (excluding furosemide), angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, antihypertensive combinations, antiadrenergic antihypertensives, and direct renin inhibitors.

Appendix E

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Appendix F

Table 2

Barriers of Medication Adherence (MA) and Findings of Quantitative studies (N=154)

Authors (Date)	Assessed Barriers[1]	Specific Measure(s) for barriers	Specific Measure(s) for MA	Definition/Scoring of MA	Key Findings[2]	
					MA	Barriers
Asthma[3] (*n*=8)						
Brandstetter et al., (2017) [1]	Patient	BMQ	MARS	MARS: - Completely MA=25 - Not completely MA=≤ 24	Completely MA=19%	Less likely to be MA: - Stronger beliefs about medication overuse by doctors (OR=0.42, 95% CI: 0.22–0.80) & harm of medicines (OR=0.43, 95% CI: 0.21–0.88) More likely to be completely MA: - Stronger beliefs about necessity of medicines (OR=2.97, 95% CI: 1.54–5.73)
Foot et al. (2019) [2]	1) Socioeconomic 2) Condition 3) Patient	BMQ, B-IPQ, MHLCS	MARS	Poor MA: ↓ MARS	M=19.2	Factors associated with MNA: - Age - Hospitalisation in last 2 years due to asthma - ↑ concerns & ↓ necessity beliefs - ↑ score on chance subscale - ↓ disease understanding
Janson et al. (2008) [3]	1) Socioeconomic 2) Condition	SPAS, MAQOL, SF-12, PCAQ, CESD	Responses on questions regarding frequency & doses	MNA: - ICS use <7 days during previous 14-days	MNA=25%	Barriers associated with poor MA: - ↓ income (OR=0.30; 95% CI: 0.10-0.93)
Makhinova et al. (2020) [4]	1) Therapy 2) Patient	ASKS-12	ASKS-12	Poor MA: ASKS-12>23	Poor MA=68.8%	Barriers to MA: - Not having an inhaler when was time to use it (92.2%) - Forgetfulness (73.4%)

						- Not having AAP/not knowing goals of therapy (65.6%) - Inconvenience (59.4%) - Irregular use of inhaler (46.9%)
Sarker et al. (2020) [5]	1) Socioeconomic 2) Therapy 3) Health-care & system 4) Patient	Pre-tested structured questionnaire	Pre-tested structured questionnaire	NR	MNA=95.6%	Factors associated with MNA: - ↑ cost of medicine - Poor counseling - Lack of family support - Lack of immediate efficacy - Forgetfulness - Knowledge on how to use device
Smits et al. (2020) [7]	1) Socioeconomic 2) Condition 3) Therapy 4) Patient	BMQ, B-IPQ	MARS-5	Poor MA: MARS>6	Poor MA= 66.1%	Factors associated with MNA: - ↑ concerns for long-term effects of medication (OR=2.0; 95% CI: 1.22–3.27) - ↓ convinced that future health depends on asthma treatment (OR=0.42; 95% CI: 0.24–0.74)
Sofianou et al. (2013) [8]	1) Socioeconomic 2) Therapy 3) Patient 4) Condition	BMQ, B-IPQ	MARS-5	Good MA: MARS score ≥4.5	Poor MA=57%	1) Sociodemographic barriers - Limited English skills & monthly household incomes below $1,350, black race, Hispanic ethnicity, ↓ education, chronic illnesses 2) Treatment beliefs: - "No symptoms, no asthma" belief - A doctor could cure asthma - No treatment benefit 3) Patient factors: - Medications are not necessary - ↑ concerns about side-effects & other problems of using medication - Believing asthma is not a chronic disease
Ulrik et al. (2006) [9]	1) Socioeconomic 2) Condition 3) Therapy	Questionnaire developed by them	Questionnaire developed by them	1) MNA: question on MA frequency forgetfulness	Accidental=27 %	Factors associated to MA: - Female gender

	4) Patient			2) Intentional vs. unintentional: question on decision not taking medication	Intentional MNA= 24%	- Believing that it is best not to forget the ICS therapy & having developed a fixed daily routine - If doctor told them it was important to take medication Factors associated to MNA: - Lack of perceived asthma symptoms - Increased disagreement that controller therapy is effective
Cancer[3] (*n*=4)						
Atkins & Fallowfield (2006) [10]	1) Socioeconomic 2) Patient	Semi-structured interview questions	Semi-structured interview questions	MNA: occasionally forget/choose not/ both to take medication	MNA=55% Intentional=17 % Unintentional= 83%	1) Factors associated with poor MA: - Younger age (t=2.48, 95% CI: 1.00–8.95) - Dislike any aspects of current medication
Neugut et al. (2016) [11]	1) Socioeconomic 2) Therapy	MPR for prior chronic medication	MPR filled by pharmacy	MPR between the first & last prescriptions of 80% or greater	MNA=15.6%	1) Sociodemographics: - Younger ages (<45 years (OR=2.00) & 45-54 (OR=1.43) 2) Participants who used ≥1 chronic medication (9.8%)
Spencer et al. (2019) [12]	1) Socioeconomic 2) Therapy 3) Health-care & system 4) Condition 5) Patient	ET-specific questionnaire	ET-specific questionnaire	NR	NR	Reasons for MNA: - 58% at least 1 barrier to MA - Just forget (27.2%) - Away from home (22.7%) - Too expensive (10.8%)
Tzeng et al. (2008) [13]	1) Socioeconomic 2) Therapy 3) Health-care & system 4) Condition 5) Patient	BQT, APS	MMAS-4	MMAS-4 - High MA=4 - Moderate=2-3 - Low=0-1	Low=51%	Significant predictors: - Age: older patients ↑MA (beta=0.23) - BQT score: ↑ score ↓ MA (beta=-0.39) - Satisfaction with clinicians: ↑satisfaction ↑MA (beta=0.37)
Diabetes & Hypertension[3] (*n*=1)						
Khayyat et al. (2019) [14]	Patient	WHOQOL-BREF	MMAS-8	MMAS-8: - Low=<6 - Medium= 6-7 - High=8	Low=54.3% Medium=24% High=21.7%	Factors associated with MNA: - ↓ quality of life

Diabetes[3] (*n*=27)						
Abade (2019) [15]	1) Socioeconomic 2) Therapy 3) Patient	OSS-3, FCQ, HADS	MMAS-8	MMAS: - 0=high MA - 1-2= medium - >2=low MA	Low MA=68.8%	Factors associated with MNA: - Living in rural (AOR=2.35; 95% CI: 1.25-3.23) - Single (AOR=3.55; 95% CI: 1.59-7.29) - Merchant (AOR=3.32; 95% CI: 1.22-9.02) - ↑ fear of complication (AOR=3.01; 95% CI: 1.66, 5.53) - Feeling worse (AOR=2.55; 95% CI:1.45-4.53)
Abdullah et al. (2019) [16]	1) Socioeconomic 2) Therapy	MCQ	MCQ	Good MA: MCQ≥27	Poor MA=44.83%	Factors associated with MNA: - Ethnicity: Malay (OR=1.43; 95% CI: 1.03-1.99) - Poor glycaemic reading (OR=2.71; 95% CI: 1.56-4.72)
Abebe, Berhane, & Worku (2014) [17]	1) Socioeconomic 2) Condition 3) Therapy 4) Health-care & system	Structured questionnaire in interviews	MMAS-8	MMAS - High MA=8 - Medium=6-7 - Low=<6	Low=25.4% Medium=28.7% High=45.9%	Barriers to poor MA: - Poor wealth status (OR=1.99; 95% CI: 1.15-3.43) - Dissatisfaction with clinic services (OR=2.23: 95% CI: 1.04-4.80) - Receive noninsulin regimen (OR=2.31; 95% CI: 1.50-3.47) - Consultation of traditional healers (OR=2.90; 95% CI: 1.03-8.15)
Aminde et al. (2019) [18]	1) Socioeconomic 2) Therapy 3) Health-care & system 4) Condition 5) Patient	MCQ	MCQ	MNA: MCQ<27	MNA=54.4%	Factors associated with MNA: - Insulin therapy (AOR=2.85; 95% CI: 1.01–8.08) - Aged > 60 years (AOR=0.48; 95% CI: 0.25–0.94) - Consuming alcohol (AOR=2.13; 95% CI: 1.10–4.14) Reasons for MNA: - Forgetfulness (30.2%) - Lack of finances (17.4%) - Disappearance of symptoms (7.7%)

						- Being too busy (7.7%)
Atekha (2018) [19]	1) Socioeconomic 2) Therapy	DKT	MMAS-8	MNA: MMAS=0-5	MNA=26.8%	- ↓ education associated with MNA
Bailey et al., (2012) [22]	1) Socioeconomic 2) Therapy 3) Health-care & system 4) Patient	1) Barriers were assessed with some questions that authors developed 2) MMAS-8	MMAS-8	MNA: MMAS=0-6	MNA=56%	Reasons for MNA: - Cost (22%) - No refills (20.3%) - Forgetfulness (11.9%) - Inadequate pharmacy stock (8.5%) - Transportation (6.8%)
Banuelos Mota et al. (2019) [23]	Patient	Developed questionnaire	Developed questionnaire	NR	NR	Factors associated with MNA: - Difficult to keep track of all medications (OR=3.3; 95% CI: 1.32-7.41) - Difficult for me to understand what each medication is for (OR=2.74; 95% CI: 1.19-6.34) - Talking too many medications (OR=2.41; 95% CI: 1.14, 5.13)
Benrazavy & Khalooei (2019) [24]	1) Socioeconomic 2) Condition 3) Therapy	MMAS-8	MMAS-8	MNA: MMAS<6	MNA=35.4%	Factors associated with ↑ MA: - Secondary/high school (OR=2.43; 95% CI: 1.53-3.87) - University education (OR=5.86; 95% CI: 2.24-15.32) - Taking insulin as monotherapy or in combination (OR=2.38; 95% CI: 1.50-3.78)
Farhat et al. (2019) [26]	1) Socioeconomic 2) Therapy 3) Condition 4) Patient	WHOQOL-BREF, TQSM, B-IPQ	Questions on frequency, percent & rating of medications	0%=Very poor MA 100%=Excellent	MNA=17.3%	Barriers to MA: - Not using pill planner (MA=88.1%) - ↑ BMI (r=-0.2) - Fasting blood glucose (r=-0.3) - ↑ IPQ score (r=-0.18) -WHOQOL-BREF: physical health (r=0.2), psychological (r=0.2), quality of life (r=0.17) & global health (r=0.15)

Gutierrez & Long, (2011) [27]	1) Condition 2) Therapy 3) Patient	HBM scales	MMAS	Good MA: MMAS=3-4	NR	- Greater perceived benefits to take medications, self-efficacy, perceived control: ↑good MA - Greater worry about side effects, perceived barriers to medication taking & ↑ belief in luck: ↑poor MA
Horii et al. (2019) [28]	1) Socioeconomic 2) Therapy 3) Health-care & system	Medical claim database	Medical claim database	MNA: PDC<0.8	MNA=50.2%	Factors associated with MNA: - Number of medications 3–4 (OR=1.68, 95% CI: 1.07–2.64) or ≥5 (OR=2.74, 95% CI: 1.38–5.46) - Male sex (OR=0.45, 95% CI: 0.23–0.89) - Age ≥50 & <60 years (OR=2.15, 95% CI: 1.15–3.99) - Total number of visits ≤17 (OR=29.9, 95% CI: 18.4–48.7)
Jaam et al. (2018a) [29]	1) Socioeconomic 2) Patient 3) Therapy	Questionnaire developed to assess barriers to MA	ARMS-D	ARMS-D: >11=MNA	MNA=73%	1) Sociodemographic characteristics: - Ages<65 - ↓ level of education - ↓ level of income - Arab ethnicity 2) Barriers to MA: - Forgetfulness (41.5%), inconvenience (36.5%), use of traditional medicine (36.5%)
Kang & Hur (2019) [32]	1) Socioeconomic 2) Therapy 3) Patient	DM-KS, SES, DLC	MMAS-8	MMAS: - <6=low MA - 6-8=medium - 8=high MA	Low=30.3% Medium=59.4% High=10.3%	Factors associated with ↑ MA: - Having a job (β=.16, p<.05) - Shorter duration of illness (β=−.18, p<.05) - ↑ self-efficacy (β=.19, p<.05)
Kretchy et al. (2020) [163]	1) Socioeconomic 2) Therapy 3) Patient	PAIDQ	MARS	Low MA: MARS<25	Low MA=66.5%	Factors associated with MNA: - ↑ distress (OR=0.32; 95% CI: 0.15-0.65)

Mohd et al. (2016) [34]	1) Socioeconomic 2) Condition 3) Therapy 4) Patient	DASS, IPAQ, MMAS-8	MMAS-8	MMAS-8 - MNA=< 6 - Medium=6-7 - High=8	MNA= 64.6% Medium=26.5% High=9.0%	Barriers to MA: - Younger age (OR=1.11) - Male gender (71.8% MNA) - Emirati patients (81.6% MNA) - Primary/secondary school education (OR=19.6) - Married (66% MNA) - ↓ physical activity (75.7% MNA) - ↓ duration of diabetes (OR=1.83) - ↓ combination therapy (68.1%) - More likely to use Insulin (58.7%) - ↓ other chronic conditions (46.9%) - ↑ depression (39.6%), severe anxiety (29.2%), severe stress (20.1%) MNA reasons: - Difficulty remembering taking medications (88.8%) - Symptoms under control (58.5%) - Forget to take medications with them (49.3%) - Feeling hassle to follow treatment (45.7%) - Forgetfulness (39.5%) - Did not take medications 2 weeks before the interview (37.9%) - Worsening of symptoms (33.4%)
Nelson et al. (2018) [35]	1) Socioeconomic 2) Patient	1Card-sorting task	ARMS-D, SDSCA-MS	1) ARMS-D: ↑ score → ↑ MA 2) SDSCA-MS: ↑ score→ ↑ days MA	No MA barriers=7%	1) Younger age: ↑ barrier scores 2) Barriers to MA: - Personal motivation barriers (2.4±1.7) - Forgetfulness (49%) - Thinking brand name medicine works better than generic (40%) - Being disappointed when medicine doesn't improve diabetes right away (37%) - Feeling burned out with having to take medicines (36%)

Nonogaki et al. (2019) [36]	1) Socioeconomic 2) Therapy 3) Condition 4) Health-care & system	Guide to developing knowledge, attitude, and practice survey	MMAS-4	MMAS: - 0=high MA - 1-4= medium-low MA	Medium-low MA= 50.7%	Factors associated with ↑ MA: - ↑ family income (>50 USD per month; AOR=5.00, 95% CI: 2.25–11.08) - Absence of diabetes mellitus-related complications (AOR=1.66, 95% CI: 1.19–2.32) - Use of health services ≥ once per month (AOR=2.87, 95% CI: 1.64–5.04) - Following special diet for diabetes (AOR=1.81, 95% CI: 1.17–2.81) - Absence of alcohol consumption (AOR=13.67, 95% CI: 2.86–65.34)
Odegard & Gray (2008) [37]	1) Socioeconomic 2) Patient	BMQ	Baseline MA with a two-question technique	Two-question recall technique on remembering to take & forget medication	47% difficulty with MA	MA challenges: - Paying for medications (34%) - Remembering doses (31%) - Reading prescription labels (21%) - Obtaining refills (21%)
Park et al. (2010) [38]	1) Socioeconomic 2) Condition 3) Therapy 4) Patient	1) Questions by authors	MMAS-4	MNA: MMAS≥1 "yes"	MNA: -8.9% tertiary hospital -6.8% private clinic	1) Sociodemographic & lifestyle variables - ↑ financial level in clinic patients - Health insurance security program in clinic patients → ↓ MA 2) Disease & medication characteristics - ↑ self-efficacy→ ↑ MA - In tertiary hospitals patients, drug storage condition & self-high efficacy - In private clinic patients, severity for diabetes complications & self-efficacy 3) Susceptibility, severity, benefit, barrier, cues to action, self-efficacy - ↓ barrier to hospital use → ↑ MA in tertiary hospitals - Recognizing complications caused by diabetes are very serious → ↑ MA in private clinic - Cue to action → ↑ MA

Pereira et al. (2019) [40]	1) Therapy 2) Condition 3) Patient	BMQ, B-IPQ	MARS	↑ MARS → ↑ MA	NR	Factors associated with ↑ MA: - Weaker general beliefs about medicines - Stronger needs about medicines - Perception of greater consequences of diabetes - Greater control over disease and treatment - Greater symptoms - Perception of greater concern about diabetes - ↑ emotional impact of disease
Peres et al. (2020) [41]	1) Socioeconomic 2) Therapy 3) Condition	CD, CP, MT	MGT	Compliant: MGT>80%	MNA=36.8%	Factors associated with MNA: - ↑ depression (OR=2.8; 95% CI: 1.2–6.5)
Rezaie, Laghousi & Alizadeh (2019) [43]	1) Socioeconomic 2) Condition 3) Therapy 4) Patient 5) Health-care & system	MMAS-8	MMAS-8	MMAS: - <6=low MA - 6-8=moderate - 8=high MA	Low MA= 85% Moderate= 14.1% High= 0.9%	Factors associated with MNA: - Female gender (OR=2.11; 95% CI: 1.03-4.32) - Living alone (OR=2.88; 95% CI: 1.38-6.04) - Living in urban (OR=0.48; 95% CI: 0.25-0.91) - Lacking insurance (OR=0.34; 95% CI: 0.14-0.85) - Diabetic complications (OR=0.48; 95% CI: 0.24-0.95) - Unemployment (OR=0.09; 95% CI: 0.09–0.9) Reasons for MNA: - Lack of suitable place & time for physical activity - Difficulty in maintaining recommended diet - Limited access to physicians
Shams et al. (2016) [44]	1) Socioeconomic 2) Condition 3) Therapy	1) MMAS-8 2) MDKT	MMAS-8	MNA: MMAS score <6	37.7% MNA	Reasons for MA - Feeling hassle to follow treatment plan (79%)

	4) Patient					- Forgetfulness (49%) - Stop taking medicines due to worsening of symptoms or side effects (32%) - Didn't take medicines along with them (45%) - Feeling better (16%) MNA was associated with: - Poor diabetes knowledge - Illiteracy - Poor glycaemic control - Poly-pharmacy - Use of other modes of therapy
Shiyanbola & Nelson (2011) [45]	1) Condition 2) Therapy 3) Patient	1) IPQ-R 2) BMQ	MMAS-4	MA: MMAS score ≤ 1	56.3% MNA	Disease perceptions associated with MNA: - Beliefs that actions can control disease (r=-0.52)
Sweileh et al. (2014) [46]	1) Socioeconomic 2) Patient 3) Therapy 4) Condition	1) BMQ 2) MDKT 3) MMAS-8	MMAS-8	MNA: MMAS <6	42.7% MNA	Sociodemographic characteristics: - Married → ↓ MNA (OR=0.6; 95% CI, 0.4-0.9) - ↑ diabetes-related knowledge (OR=0.8; 95% CI 0.7-0.9) MNA reasons: - Difficulty remembering to take all medications (73.9%) - Forgetfulness (38%) - Forget to take medications with them (33.1%) - Feeling hassle to follow treatment (34.6%) - Did not take medications two weeks before the interview (24%) - Worsening of symptoms (18%) - Symptoms under control (17%) Medication beliefs associated with MNA: - Medications are harmful (51%) - ↓ specific-necessity

						- ↑ specific-concern - ↑ general-harm
Tristan (2015) [47]	1) Socioeconomic 2) Condition	Electronic medication record database	Electronic medication record database	MNA: failure to comply with medication last 6 months	MNA=46.5%	Gender (OR=0.41) - Male gender → ↓ MA (68.3%) Health education (OR=1.90) - Patients who take health educational classes → ↑ MA (51.9%)
Zioga et al. (2016) [48]	1) Socioeconomic 2) Condition 3) Therapy	DSCAQ, SF-36	Diabetes Self-Care Activities Questionnaire	NR	NR	- Best MA values relate to diet (4± 1.62), blood test–blood sugar tests (4.98± 2.53) & recommendations on self-care activities (3.27±0.93) - ↑ QOL→ ↑ MA
Epilepsy[3] (*n*=10)						
Chapman et al. (2014) [49]	Patient	1) BMQ 2) PSM	1) ESMS 2) MPR	MNA: ESMS<8 & MPR<0.8	MNA=36.7%	Patient beliefs associated with MNA: - Fewer beliefs in personal need for medication (OR=0.61, 95% CI: 0.46-0.80) - ↑ concerns about potential adverse effects (OR=1.42, 95% CI: 1.09-1.85) - Medicines are more overused (OR=1.43, 95% CI: 1.11-1.85) - Medicines are harmful (OR=1.62, 95% CI: 1.12-2.35)
Egenasi, Steinberg, & Raubenheimer (2015) [50]	Patient	BMQ	MMAS-8	MMAS: - 0-2 high MA - >3 low MA	Low MA=45.4%	Beliefs on medication: - ↑ Patient concerns about medications ↓ MA (r=0.35) - ↑ Belief in the necessity of medication ↑using medication (r=-0.14) - ↑ Belief medication might be harmful ↑not continue with medication (r=0.24)
Elsayed et al. (2019) [51]	1) Therapy 2) Patient	BMQ	MMAS-4	MNA: MMAS≤1	MNA=35.4%	Factors associated with MNA: - Forgetfulness - Side effects - ↓ necessity score

						- ↑ concern score
Fadaye-Vatan et al. (2017) [52]	1) Socioeconomic 2) Therapy 3) Condition	MPK	MARS	MA: MARS ≥ 6	MNA=21.8%	1) Sociodemographic characteristics: - Widowhood, divorcehood 2) Factors associated with MNA: - Positive comorbid state - Side effects
Getnet et al. (2016) [53]	1) Condition 2) Therapy 3) Health-care & system 4) Patient	OSS-3, KSS	MMAS-8	MMAS= MNA (Yes/No)	MNA=37.8%	Factors associated with MNA: - Being on treatment for 6 years & above (AOR=3.47, 95% CI: 1.88-6.40) - Payment for AEDs (AOR=2.76, 95% CI: 1.73-4.42) - Lack of health information (AOR=2.20, 95% CI: 1.41-3.43) - Poor social support (AOR=1.88, 95% CI: 1.01-3.50) - Perceived stigma (AOR=2.27, 95% CI: 1.47-3.56), - Side effects (AOR=1.70, 95% CI: 1.06-2.72)
Gurumurthy, Chanda, & Sarma (2017) [54]	1) Socioeconomic 2) Patient	Case record form, MMAS-4	MMAS-4	MMAS: MNA≤ 2	MNA=27.7%	1) Sociodemographic characteristics associated with ↑ MA: - Middle/lower-middle socioeconomic class (OR= 0.52, 95% CI: 0.32–0.84) - Focal epilepsy (OR=0.62, 95% CI: 0.40–0.95) 2) Reasons for MNA: - Forgetfulness (32.5%), having problems remembering (29.3%), feeling worse (20.0%), feeling better (18.2%)
Honnekeri et al. (2018) [56]	1) Therapy 2) Patient 3) Condition	LSSS, QOLIE-31	MARS-5	High MA: MARS≥20	MNA=48.7%	Factors associated with MNA: - Seizure severity (β=–0.33, p<0.0001) - Serum AED level (β=0.29, p<0.0001) - Quality of life (β=0.30, p<0.0001)

Paschal, Rush, & Sadler (2014) [57]	1) Socioeconomic 2) Therapy 3) Health-care & system 4) Condition 5) Patient	Questionnaire developed, B-IPQ, WHOQOL-BREF	Yes/no question	Yes/No question if MA	MNA=9.9%	1) Socioeconomic: - Monthly cost of medication 2) Therapy factors: - Number of times forgot to take medications - Number of times stopped taking medication 3) Health system- & provider-related factors: - Duration of non-availability of medication 4) Psychosocial factors: - Perception of health status 5) Perception of illness: - Poor perception of disease
Shaaban, Ishak, & Ismail (2011) [58]	1) Socioeconomic 2) Patient 3) Therapy 4) Health-care & system	Questionnaire developed	Missed/skipped medication doses	Increased MA: fewer missed/ skipped medication doses	66% missed taking medication monthly	1) Sociodemographic characteristics - ↓ educational attainment 2) Reasons for MNA - Forgetfulness (68%), cost (5%), side effects (3%) 3) Factors that facilitate MA - Medication reminder strategies (46%)
Shahraki et al. (2019) [55]	1) Socioeconomic 2) Therapy 3) Health-care & system	NR	NR	MA: Score≥ 40	MNA=52.2%	Factors associated with MNA: - Patient understanding - Complexity of drug regiment - Cost & physical changes of medication
HIV[3] (*n*=69)						
Abdulrahman et al. (2017) [59]	Socioeconomic	AACTG	AACTG	Optimal MA: MA≥95% Suboptimal: MA<95%	Suboptimal MA= 64.5%	Factors associated with MNA: - Living in rural locations (OR=2.46; 95% CI: 1.04-5.85) - <bachelor degree (OR=2.25; 95% CI: 1.20-4.20) - ↓ monthly income (OR=3.60; 95% CI: 1.32-9.85) - Unemployed (OR=4.64; 95% CI: 1.09-19.82)

Achappa et al. (2013) [60]	1) Socioeconomic 2) Patient 3) Therapy 4) Condition 5) Health-care & system	AACTG , BDI	AACTG	Low MA=<95% High= ≥95%	Low=36.3% High=63.7%	Reasons of MNA: - Forgetfulness (33%) - ↑ cost (30%) Factors associated with MNA: - Lack of family care - Depression - Consumption of alcohol - Social stigma - Side effects
Amberbir et al. (2008) [61]	1) Patient 2) Therapy 3) Condition	Pre-tested questionnaire	Patient's report on doses missed	Adherers: ≥95%	MNA= 20.8%	Reasons for MNA: - Forgetfulness (43.7%) - Felt sick or ill at that time (19.5%) - Ran out of medication (12.6%) Factors associated with ↑ MA: - Social support (OR=1.82, 95% CI: 1.04-3.21) - ↓ depression (OR=2.13, 95% CI: 1.18-3.81)
Anyaike et al. (2019) [62]	1) Socioeconomic 2) Patient 3) Therapy 4) Health-care and system	AACTG	Patients' report on number of pills missed	MNA: <95%	MNA= 10.2%	Reasons and factors associated with MNA: - No formal education (21.9%) - Travelling outside nation (44.4%) - Felt sick and depressed (25%) - Ran out of drugs at home (33.3%) - Felt better (5.6 %) - Lack of money for transportation (50%) - To avoid side effects (37.5%) - Forgetfulness (41.7%) - Not want to be seen in the clinic collecting drugs (30.5%) - Could not refill their drugs because of unscheduled public holidays by government (19.8%) - No support from friends and family
Beer & Skarbinski (2014) [65]	1) Socioeconomic 2) Patient	AACTG	AACTG	1)Dose MA= 100% MA	Overall MNA: 40%	Factors associated with MNA:

	3) Therapy 4) Condition			2) Schedule MA= MA to medication schedule 3) Instructions MA=MA to special instructions	Dose MNA: 14% Schedule MNA: 28% Instructions MNA: 31%	- Younger age (ages 18-29 & 30-39) (aPR=0.86, 95% CI: 0.79-0.94) - Female gender (aPR=0.96, 95% CI: 0.93-0.99) - Depression (aPR=0.96, 95% CI: 0.93-1.00), - Stimulant drugs use (aPR=0.87; 95% CI: 0.81-0.92) - Binge alcohol use (aPR=0.90, 95% CI: 0.86-0.94) - Greater than once-daily dosing (aPR=0.95, 95% CI: 0.92-0.98) - Longer time since HIV diagnosis (≥10 years) (aPR=0.95, 95% CI: 0.91-0.98) - Side effects (aPR=0.95, 95% CI: 0.90-0.99) - Patient beliefs (e.g., unsure if taken medication as directed or body will become resistant)
Boretzki et al. (2017) [67]	1) Socioeconomic 2) Patient 3) Therapy 4) Condition	Questionnaire developed	Questionnaire developed	1) Good MA: Excellent history of MA 2) Unstable MA: Intermittent phases of MNA 3) Poor MA: Rarely MA	Good MA: 75% Unstable MA: 7% Poor MA: 8%	Factors associated with unstable or poor MA: - Age <30 years (OR=4.2, 95% CI: 1.4–12.6, p<0.05) - HIV transmission via intravenous drug use (OR=16.7, 95% CI: 4.2–66.2, p<0.01) - History of AIDS (OR=5.8, 95% CI: 2.2–15.3, p<0.01) - Psychiatric disorders (OR=2.5, 95% CI: 1.2–5.4, p<0.05) Reasons for MNA: - Forgetfulness - Reminder of the disease - Skipping medication when feeling bad - Stress/stressful work - Interactive toxicity beliefs regarding alcohol or party drugs/going out - Different daily routine - Afraid of being seen

Buscher et al. (2013) [68]	Therapy	Questionnaire developed	30-day VAS scale	No specific definition used	Median MA: Once daily regimens= 99.5% Twice daily regimens= 94% Fixed dose combination= 100%	- ↑ MA in once daily dosing of ART vs. twice daily dosing
Chime, Onyemaechi, & Orji (2019) [69]	1) Socioeconomic 2) Patient 3) Therapy 4) Condition	Pre-tested semi structured questionnaire	Pharmacy records, self-report	Poor MA: MA<95%	Poor MA=10.5%	Reasons for MNA: - Being away from home (41.8%) - Forgetfulness (35.0%) - Physical discomfort (6.8%) Factors associated with ↑ MA: - ↑ duration in treatment (AOR=1.92; 95% CI: 1.17–3.16) - Not consuming alcohol (AOR=3.67, 95% CI: 2.01–6.70) - Not consuming traditional medicine (AOR=2.76; 95% CI: 1.33–5.73) - Resided in urban areas (AOR: 1.90; 95% CI: 1.17–3.06)
Do et al. (2010) [71]	1) Socioeconomic 2) Patient 3) Therapy 4) Condition	KPS, EQ-5D, BDI	Patients' 4 day & 1 month recall, & institutional MA	MA: no missed ARV medication doses in past 4 days, past 1 month & refill visits during past 3 months	MNA=18.7%	Reasons for MNA: - Forgetfulness (20.6%) - Feeling healthy (7.6%) - Experiencing active toxicities that made them feel worse (3.3%) Factors associated with MNA: - Presence of depression - Active alcohol use - Failure to disclose HIV status to partner
Dworkin et al. (2016) [72]	1) Socioeconomic 2) Patient 3) Therapy 4) Condition	11-item scale	Patients' report on doses missed	MNA: missed > single dose of HIV medication in previous 2 weeks	MNA= 20%	Factors associated with MNA: - Older age - Female sex - Moderate to severe depression

	5) Health-care & system					- ↓ self-worth - ↓ acceptance of HIV diagnosis - ↓ understanding of need to adhere to HIV medication Reasons of MNA: - Forgetfulness - Traveling away from home
Dyrehave et al. (2016) [73]	1) Socioeconomic 2) Patient 3) Therapy 4) Condition	AACTG, HIV-related knowledge questions	AACTG	Adherers: ≥95% MA in past 4 days	MNA=24.9%	Reasons for MNA: - Forgetfulness (23%) - Side effects (15%) - Lack of food (8%) - Being too ill to attend the clinic (4%) Factors associated with MNA: - Treatment perceptions - You can be cured of HIV by traditional medicine (OR=1.7, 95% CI: 1.0-2.9; p<.05) - No treatment for side effects (OR=0.6, 95% CI: 0.4-1.0; p<.05) - ↓ illness-related knowledge - HIV is contracted because of traditional causes (OR=1.9, 95% CI: 1.1-3.0; p<.05)
Ferguson et al. (2002) [75]	1) Socioeconomic 2) Patient 3) Therapy 4) Condition	PMAQ, questionnaire on barriers	PMAQ	MA=100% in past 4 weeks	MA: 34.8% MNA: 65.2%	Barriers to MA: - Taking ↑ medicines than wanted - Taking medicines was a reminder of HIV status - Uncomfortable for other people to know medicines were for HIV/AIDS - Not want to be seen taking medications - Medicines were hard to swallow - Caucasians (OR=5.64; 95% CI: 1.37-23.27)
Gauchet, Tarquinio, & Fischer (2007) [76]	1) Socioeconomic 2) Patient 3) Therapy 4) Condition	Values scale, BMQ	MA scale	↑score ↑ MA	NR	Factors associated with ↑ MA: - Greater confidence in physician - Stronger beliefs about necessity of ART

	5) Health-care and system					- ↓ belief that medicines are harmful - Confidence with therapy - Duration of treatment - Duration of HIV infection
Gianotti et al. (2013) [77]	1) Socioeconomic 2) Patient 3) Therapy 4) Condition	MA and health status questionnaire	MA and health status questionnaire	No definition used	100% MA= 79% MA>95%= 80%	Factors associated with MA: - Health status (r=0.21; p<0.0001) - Current CD4 cell count (r=0.06; p<0.01) - Health status (r=–.09; p<0.0001) - Age (r=–.11; p<0.0001) - Male gender [94.5% (16.4%) *vs.* 92.8% (19.5%); p<0.05]
Gordillo et al. (1999) [78]	1) Socioeconomic 2) Patient 3) Condition	BDI, HADS-A	Pill count, self-report	Good MA: MA>90%	Good MA=57.6% MNA=42.4%	Factors associated with good MA: - Older ages (i.e., 32-35; OR=2.31; 95% CI: 1.21–4.40) - ↑ education level (OR=4.0; 95% CI: 1.10-14.50) - Employment (OR=2.24; 95% CI: 1.27–2.73) - Good social support (OR=2.03; 95% CI: 1.26–3.27) - Lack of depression (OR=1.79; 95% CI: 1.27–2.73)
Grierson et al. (2011) [79]	1) Socioeconomic 2) Patient 3) Therapy 4) Condition 5) Health-care & system	HIV Futures 6 survey	HIV Futures 6 survey	NR	Difficulty taking ART: 39.1%	Reasons of MNA: - Remembering to take drugs on time (20.1%) - Experience side effects (18.9%) - Carrying medication (15.1%) Factors associated with MNA: - Younger age - Alcohol and party drug use - Poor or fair self-reported health - Diagnosis of mental health condition - Living in regional centre - Taking ≥1 dose per day - Experiencing physical adverse events - Types of ART regimen

						- Specific attitudes towards ART and HIV
Gust et al. (2011) [80]	1) Socioeconomic 2) Patient 3) Therapy 4) Condition 5) Health-care and system	Focus group discussions & interviews	Pharmacy refill	MNA: 1) refusal to take any more medication 2) agreeing to attend quarterly visits 3) seen at last expected visit	MNA=22%	Barriers to MA: - Work commitments - Side effects - Started ART - Stigma - Relocate - Lack of staff - Transport - Inconsistent Factors associated with MNA: - Male (AOR=2.24; 95% CI: 1.24–4.04) - Difficulties with the regimen (AOR=3.40; 95% CI: 1.75–6.60) - Older ages (AOR=0.94; 95% CI: 0.91–0.98) - Having a secondary education (AOR 2.55; 95% CI: 1.10–5.91) Reasons for MNA: - Work commitments (18.9%) - They thought that completed study (17.3%) - Side effects (15.8%)
Harris et al. (2011) [81]	1) Socioeconomic 2) Patient 3) Condition	AACTG	VAS scale	Optimal MA: ≥95% MA in past 1 month	Suboptimal MA= 24%	Factors associated with MNA: - Heavy alcohol consumption (OR=2.5; 95% CI: 1.4–4.5) - Having children (OR=2.2; 95% CI: 1.1–4.9) - Lack of perceived family support - Lack of perceived MA support (OR=2.0; 95% CI: 1.1–3.6) Reasons for MNA: - Forgetfulness (41%) - Being away from home (31%) - Running out of medications (21%)
Holstad, Pace, & De (2006) [82]	1) Socioeconomic 2) Patient	AGAS, SCI, SWB, SIBS, AADQ	AGAS	Low MA: AGAS=10	Mean MA=24.9%	Factors associated with MA:

	3) Therapy 4) Condition 5) Health-care and system					- Positively correlated with SB (r=0.34, p<0.05), INT (r=0.19, p<0.05), PU (r=0.25, p<0.05) - Negatively correlated with years HIV-infected (r=0.27, p<0.05), years on ART (r=0.21, p<0.05), perceived health status (r=0.20, p<0.05)
Holzemer et al. (1999) [84]	1) Patient 2) Condition 3) Health-care and system	SSC-HIV, CESD, SF-36, Various scales	MGL	4=MNA	Mean MNA=1.59	Factors associated with MNA: - Health illness: ↑ symptoms e.g., depression, ↓ quality of life Facilitators of MA: - Having a meaningful life - Taking time for important things
Kalichman et al. (2016) [85]	1) Socioeconomic 2) Patient 3) Therapy 4) Condition	CESD, AUDIT, BMQ	Pill count	MA=85% during previous 6 weeks	MNA=34.5%	Factors associated with MNA: - Poorer health - Food insecurity - Lack of transportation - ↑ depression - Greater alcohol use - Illicit drug use - Greater concern beliefs for medications - Fewer beliefs that taking medications are necessary for health
Khalili et al. (2012) [86]	1) Socioeconomic 2) Patient 3) Therapy 4) Condition 5) Health-care & system	Medical records	1. Question on number of medications consumed in previous 4 days 2. Pill count	MNA: MA<95%	MNA: - Self-report: 34.5% - Pill count: 39.6%	Reasons of MNA: - Adverse effects (26.1%) - Forgetfulness (15.4%) - Unavailability of ART (13%) Factors associated with MA: - Older ages → ↑ MA (r=0.32; p<0.01). - Living with family members → ↓ MA - Advanced stage of disease (Stage C) → ↓ MA - Changing medication → ↓ MA
Kioko & Pertet (2017) [87]	1) Socioeconomic 2) Patient 3) Therapy	PMAQ	1) Participants' report on medication missed over past 7 days 2) Pill count	MNA=<95%	Self-report MNA: 14.4% Pill count MNA:	Reasons for MNA: - Side effects (28.8%) - Travelling (14.7%) - Forgetfulness (6.7%)

					43.5%	Factors associated with MA: - Marital status (divorced ↑ MA) (χ^2=10.3, p<0.05) - Social support (patients with a good perception of social support ↑ MA) (OR=2.5, 95% CI: 1.3–3.6) - Side effects (χ^2=68.31, p≤.001)
Kremer, Ironson, & Porr (2009) [89]	Patient	AACTG	AACTG	% of missed doses over last 3 days	M=1.89	Factors associated with ↑ MA: - Spiritual beliefs e.g., spirituality helps coping with side effects - Mind-body beliefs e.g., mind helps MA
Legesse & Reta (2019) [92]	1) Socioeconomic 2) Patient 3) Therapy 4) Condition	AACTG	Patients' report of 7 days recall of missed doses	Poor: MA<95%	Poor=28.2% Good=71.8%	Reasons of MNA: - Forgetfulness (53.4%) - Transportation (22%) - Refusal to take drugs (13.6%) - Illness (11%) Factors associated with MNA: - Disclosure HIV status to families (AOR=0.12, 95% CI: 0.05-0.58; p<0.001) - Encounter of drug side effect (AOR=2.69, 95% CI: 1.27-5.05; p<0.001)
Letta et al. (2016) [93]	1) Socioeconomic 2) Patient 3) Therapy 4) Condition	CESD, questionnaire developed	Patients' report on 7 day recall dose MA	MA= taking all pills at right time	MNA=15%	Reasons for MNA: - Forgetfulness (39.8%) - Being away from home (21.5%) - Being busy with different activities (9.7%) Factors associated with ↑ MA: - 35–44 ages (AOR=2.39; 95% CI: 1.15–5.01) - Average income of 501–999 ETB per month (AOR=6.73; 95% CI: 2.71–16.75) - Taking 2 tablets (AOR=12.98; 95% CI: 2.78–60.59), 3 tablets (AOR=12.90; 95% CI: 2.87–57.94) & 4 tablets

						(AOR=5.87; 95% CI: 1.02–28.54) vs. ≥5 tablets - History of opportunistic infection (AOR=2.81; 95% CI: 1.47–5.36) - Good family support (AOR=2.61; 95% CI: 1.45–4.72)
Leyva-Moral et al. (2019) [94]	1) Socioeconomic 2) Patient 3) Therapy 4) Condition	PLHIV-Pro, SMAQ	SMAQ	MNA: <90%	MNA= 58.3%	Reasons of MNA: - Forgetfulness (43.3%) - Experience side effects (51.1%) Factors associated with MNA: - Discomfort with treatment regimen (RP=1.38; 95% CI: 1.07–1.78; p<0.05) - Stopping treatment any time (RP=2.55; 95% CI: 1.91-3.41, p<0.001) - Stopping treatment for up to 9 days (RP=1.57; 95% CI: 1.03–2.39, p<0.01) - Concurrent tuberculosis (RP=5.19; 95% CI: 1.42–18.91; p<0.05) -Feeling sick during (RP=2.73; 95% CI: 1.24–6.00; p<0.05) - Stopping ART at some point (RP=17.17; 95% CI: 7.19–41; p<0.001) Facilitators of MA: - Having children (RP=0.25; 95% CI: 0.08–.84; p<0.05)
Li et al. (2014) [95]	1) Socioeconomic 2) Patient	BPS, MSPSS	MMAS	High MA=8 Medium=6-7 Low= ≤5	High=20.3% Medium=76.6% Low=3.1%	Factors associated with MNA: - Age - ↓ perception of health - Thai ethnicity → ↑ MA - ↑ HIV-related stigma
Maneesriwongul & Tulathong (2006) [96]	Therapy	Structured questionnaire	VAS scale	MNA=<95%	MA=>80%	Reasons of MNA: - Forget (36%) - Have activities outside home (33%), - Worried that others would notice (24%) - Sleep through the dose-time (20%) - Too busy (16%)

						- Change in daily schedule (9%) Factors associated with MA: - Undetectable viral load associated with MA ≥95% (OR=3.0; 95% CI: 1.3, 7.1; p<0.05) - ↓ number on ARV (22 vs. 32 months; p<0.05)
Masa et al. (2017) [97]	1) Socioeconomic 2) Patient 3) Health-care and system	Survey questionnaire	Pharmacy records & VAS	MNA=<95%	MNA= 30%	Factors associated with MNA: - Debt - Non-farming related occupations - Owning lands - Inadequate access to food - Place of residence (i.e., from Lumezi) - Self-perceived health status as poor
Mizuno, Beer, Huang, & Frazier (2017) [98]	1) Socioeconomic 2) Patient 3) Therapy 4) Condition 5) Health-care and system	AACTG, PHQ-8	AACTG	1) Dose MA: 100% of ART in past 3 days 2) Schedule MA: all ART doses on schedule in past 3 days 3) Instruction MA: all special instructions for ART in past 3 days	Dose MA=80% Schedule MA=71% Instruction=67 % Total MA=56%	Factors associated with MNA: - Age 30-39 vs. ages 40+ (aPR=0.76, 95% CI: 0.63-0.92) - No health insurance coverage (aPR=0.80, 95% CI: 0.66-0.97) - Depression (aPR=0.82, 95% CI: 0.70-0.95) - ↓ self-efficacy (aPR=0.59, 95% CI: 0.42-0.84)
Mo & Mak (2009) [99]	1) Socioeconomic 2) Patient 3) Therapy 4) Condition	AACTG, Self-stigma scale, Brief COPE, MHI, PSH	AACTG	MA: 1) Taking medication most of time 2) Following time, dose of medications & dietary instructions most of time in past 4 days	MA= 26.5% MNA= 73.5% Intentional MNA= 20.6% Unintentional MNA=52.0%	Factors associated with MNA: - Younger ages - Longer length of diagnosis & starting medication longer → ↑unintentional MNA - ↑ stigma level, avoidant coping, & worse mental health → ↑ unintentional MNA

				3) Not skipped medication over past weekend 4) Rarely missing/ alternating doses		
Mukui et al. (2016) [100]	1) Socioeconomic 2) Patient 3) Therapy 4) Condition 5) Health-care and system	Questionnaire developed	ARV biomarker, self-report in past 30 days	MNA: not having ARV biomarker present	MNA=9.4%	Factors associated with MNA: - Younger persons aged 15-29 years (95% CI: 10.3-37.0) - Primary/lower level of education (95% CI: 6.2-21.8) - Residing in rural areas (95% CI: 7.4-21.5) - No HIV-positive partner in past year (95% CI: 5.6-17.2) - Engaging in high-risk behavior (95% CI: 1.5-40.5) - Using recreational drugs in past month (95% CI: 2.2-55.4)
Muya et al. (2015) [103]	1) Socioeconomic 2) Patient 3) Therapy 4) Condition	Case report forms	ART pickup visits	MNA: ≥5% noncompliance with scheduled ART pickup visits	MNA=19%	Factors associated with MNA: - Younger age (RR of ≤30 years vs. ≥50 years=1.07, 95% CI: 1.05–1.09) - Advanced disease stage (RR for stage IV vs. stage I=1.04, 95% CI: 1.01–1.07) - ↑ BMI (RR for ≥30 kg/m^2 vs. <18.5=1.09, 95% CI: 1.07–1.12) - Longer duration on ART (RR=2.62, 95% CI: 2.55–2.69) - Perceived low social support (RR=0.91, 95% CI: 0.86–.95) Factors associated with ↑ MA: - Attendance at clinics in Temeke district (RR=1.11, 95% CI: 1.09–1.12)
Nakimuli-Mpungu et al. (2009) [104]	1) Socioeconomic 2) Therapy 3) Condition	SQR-20, sociodemographics	Patients' report on number of missed doses	MNA: MA<90% since initiation of treatment & previous month	MNA since initiation=30%	Factors associated with MNA: - Psychological distress (OR=3.66, 95% CI: 1.39 - 9.78)

					MNA in previous month=17.2%	- Living alone (OR=9.80, 95% CI: 2.27-18.70)
Ncama et al. (2008) [105]	1) Socioeconomic 2) Patient	MOS SF-36, MOS-SSS, AACTG	MMAS	MMAS: - 0-2=low MA - 3-4=high MA	High MA=79% Low MA=21%	No sign. differences on social support & QoL
Nduaguba et al. (2017) [106]	Patient	Various questions on barriers, therapy satisfaction	Patients' report	1) Fully MA: 100% 2) Not fully: <100% 3) Optimally: ≥95% 4) Not optimally: <95%	Fully=79.5% Not fully=20.5% Optimally=92.9 % Not optimally= 7.1%	Reasons for MNA: - Forgetfulness - Running out of medication - Improvement in health Factors associated with MNA: - Dissatisfaction with therapy (OR=0.33, 95% CI: 0.11-0.99)
Negash & Ehlers (2013) [107]	1) Socioeconomic 2) Patient 3) Therapy 4) Condition	Interviews	Interviews	MNA=<95%	MNA=26.5%	Factors associated with MNA: - Male gender - People with internalized or perceived stigma - Experiencing discrimination - Depression - ↑ alcohol consumption
Negash et al. (2016) [108]	1) Socioeconomic 2) Patient 3) Therapy 4) Condition 5) Health-care and system	Pre-tested questionnaire	Pre-tested questionnaire	Patients' report on doses missed during past month	Good MA=89.3% Poor MA=10.7%	Reasons for MNA: - Simply forgot (7.3%) - Being away from home (4.7%) - Drug was toxic or harmful (1.3%) Factors associated with MNA: - Taught college and above (AOR=0.10, 95% CI: 0.01-0.35) - Distance of ≥90 km from healthcare facilities (AOR=16.03, 95% CI: 2.43-11.48) - Depressed mood (AOR=5.72, 95% CI: 1.49-21.95)
Neupane et al. (2019) [109]	1) Socioeconomic 2) Patient 3) Therapy	AACTG	AACTG	Optimal MA: MA≥95%	Optimal MA: 87.4%	Factors associated with ↑ MA: - Females (AOR=10.55; 95% CI: 1.85, 60.05)

	4) Condition			Less than optimal: MA<95%	Less than optimal: 12.6%	- Nuclear families (AOR=4.88; 95% CI: 1.25, 19.08). - No alcohol consumption (AOR=5.84; 95% CI: 1.29, 26.38) - Duration of HIV > 3 years (AOR=10.06; 95% CI: 2.38, 42.43) - Not experiencing side effects (AOR=8.83; 95% CI: 2.06, 37.89) - Receiving ART medicine themselves (AOR=7.86; 95% CI: 1.67, 36.10)
O'Neil et al. (2012) [110]	1) Socioeconomic 2) Patient 3) Therapy 4) Condition 5) Health-care and system	Developed questionnaire, CESD	Refill compliance	MNA=<95%	MNA=44.2%	Factors associated with MA: - Increasing age → ↑ MA (AOR=1.84, 95% CI: 1.44-2.33) - Male gender → ↑ MA (AOR=1.68, 95% CI: 1.07-2.64) - Being enrolled in a comprehensive MA assistance program → ↑ MA (AOR=4.26, 95% CI: 2.12-8.54) - Annual income <$15 000 → ↓ MA (AOR=0.47, 95% CI: 0.31-0.72) - Former and current injection drug use → ↓ MA (AOR=0.46, 95% CI: 0.29-0.73 & AOR=0.35, 95% CI: 0.20-0.58)
Odili, Obieche, & Amibor (2017) [111]	1) Socioeconomic 2) Patient 3) Therapy 4) Condition 5) Health-care & system	Developed questionnaire	Developed questionnaire	MNA: missing ≥1 dose of ART in previous month	MNA=11%	Reasons of MNA: - Forgetfulness (60.4%) - Busy daily tasks (18.3%) - Not want to be seen taking medications (11%) - Experienced adverse effects (8.7%) - Many pills to take (3.3%) - Had other diseases (5%) - Out of stock of medications (5.7%) Factors associated with MNA: - Widowed marital status (MA: 76.2%; χ^2=12.07, p<0.01) - Students (MA: 71.4%) &unemployed (MA: 76.7%; χ^2=18.92, p<0.01)

Oh et al. (2009) [112]	Socioeconomic	Developed questionnaire	Developed questionnaire	<100% MA: taking all/less medication in past 4 days, taking fewer pills per dose, ever skipping any medications or not following medication schedule	100% MA: Whites=44.2% Hispanics=31.8 Blacks=28.1% Others=21.9%	Factors associated with MNA: - Hispanics (OR=2.16; p<0.001) - Blacks (OR=1.37; p<0.05) - Viral load
Oku et al. (2014) [113]	1) Socioeconomic 2) Patient 3) Therapy 4) Condition	Semi-structured questionnaire	Patient's report on doses missed in previous 7 days	Poor MA=<95%	Poor MA= 49.6%	Reasons for MNA: - Being busy (50.6%) - Simply forgetting (48.9%) - Religious constraints (16%) - Frequent travelling (14.8%) - Depression (12.2%) - Lack of food (11.2%) Factors associated with ↑ MA: - Perceived improvement in health status (OR=2.72; 95% CI: 1.37-5.39) - Use of ARV regimens devoid of dietary instructions (OR=1.5; 95% CI: 1.07-2.06) - Non-use of herbal remedies (OR=1.8; 95% CI: 1.23-2.64)
Olowookere et al. (2008) [114]	1) Socioeconomic 2) Patient 3) Therapy 4) Condition 5) Health-care and system	Pretested questionnaire	1) Drug pickup at clinical pharmacy 2) Patients' report on 7 days recall	MNA=<95%	MNA=37.1%	Reasons for MNA: - Simply forgot (55.6%) - Fasting (31.5%) - Felt well & no longer needed medication (26.4%) - Avoid side effects (35.2%) Factors associated with MNA: - Feeling healthy (OR=2.39; 95% CI: 1.3, 4.4) - Simply forgot (OR=2.1; 95% CI: 1.3, 3.4) - Not willing to disclose HIV status (OR=1.7; 95% CI: 1.0, 2.8)

Pahari et al. (2016) [115]	1) Socioeconomic 2) Patient 3) Therapy	Semi-structured interview	Pill-count	Poorly MA: MA<90% Well-MA: MA ≥90%	Poorly MA: 23% Well-MA: 77%	Factors associated with MNA: - Duration of treatment: 7th to 12th month period of ART intake (AOR=9.5; 90% CI 1.9-47.3; p<0.05) - Non-disclosure of HIV status to family members (AOR=4; 90% CI 1.3-13; p<0.05)
Pellowski & Kalichman (2016) [117]	1) Socioeconomic 2) Patient 3) Therapy 4) Condition 5) Health-care and system	Scales on HIV, shame, social support, health behavior & stressors, CESD, AUDIT-C	Pill counts	NR	Mean MA=83.5%	Factors associated with MNA: - Male gender - ↓ CD4 cells - Greater shame - ↓ social support - ↑ alcohol use - ↓ communication about health to others - Greater use of supplements
Penedo et al. (2003) [118]	1) Socioeconomic 2) Patient 3) Therapy	NEO-PI-R, HAT-QoL	AACTG	MNA=<95% in past 4 days	MNA=28%	Factors associated with ↑ MA: - Older ages (r=0.21, p<0.05) - ↑ overall functioning (r=0.29, p<0.01) - ↑ medication worries (r=0.26, p<0.01)
Pinheiro et al. (2002) [120]	1) Socioeconomic 2) Patient 3) Therapy 4) Condition	Questionaire developed	Patients' report	MNA=<95%	MNA=43.1%	Factors associated with MNA: - Patients taking antiretroviral medications >4 times/day (OR=0.44, 95% CI: 0.20-0.94) - Self-efficacy expectation (OR=3.50, 95% CI: 1.90-6.55) - Perception of negative affect and physical concerns (OR=0.71, 95% CI: 0.53-0.95) Facilitators of MA: - Increased schooling levels (≥8 years) (OR=2.28, 95% CI: 1.12-4.66)
Pomeroy et al. (2007) [121]	1) Socioeconomic 2) Patient 3) Therapy 4) Condition	Questionaire developed	Frequency of missed doses	No definition used	Little/No difficulty taking medications=71 %	Factors associated with ↑ MA: - Fewer children in household (r=–.16, p <0.04)

	5) Health-care and system					- Receiving medical care within first year of HIV diagnosis (r=0.24, p<.004) - Currently receiving mental health services (r=0.24, p<.003) - Receiving MA information (r=0.42, p<0.0001) - Increased motivation to comply with medication due to perceived vulnerability (r=0.40, p<0.0001) - Increased motivation due to provider relationship (r=0.29., p<0.0001) - Increased social support (r=0.32, p<0.0001) - Intentions to adhere (r=0.40, p<0.0001)
Royal et al. (2009) [125]	1) Socioeconomic 2) Patient 3) Therapy 4) Condition 5) Health-care and system	SF-36, CESD, PSS, HIV 8-item scale	Patients' report on 2 or 7-day recall dose	1) 2-day MA: 100% MA (missing no doses over past 2 days) 2) 7-day MA: achieved ≥90%	2-days MNA: 11% 7-days MNA: 6%	Factors associated with MNA: - Younger ages (both 2- and 7-day) - Problems accessing medical care (7-day) - Frequent drinking (2-day) - Alcohol and drugs (2-day) - Poorer mental health (both 2- and 7-day) - Negative attitudes toward ARV - Greater risk for depression & stress - Not having health insurance (2-day)
Sangeda et al. (2018) [127]	1) Socioeconomic 2) Patient 3) Therapy 4) Condition	AACTG	VAS scale, SHCS-AQ, appointment, clinical records	MNA: 1) VAS< 95% in past month 2) SHCS-AQ: forgot 2 consecutive doses/ missing ≥1 doses 3) Appointment: delayed for >20% of scheduled days 4) Pharmacy refill: <95%	MNA: 1) VAS=13.6% 2) SHCS-AQ=31% 3)Appointment = 20.2% 4) Refill=48.2% 5) Clinical records=almost 100% MA	Reasons for MNA: - Forgetfulness (52.1%) - Traveling without medication (26.5%) Factors associated with ↑ MA: - Older age - ↓ consumption of alcohol - More advanced WHO staging - Education ≤ grade 7 - Perceiving ART benefits - ↓ weight/BMI at recruitment - ↓ alcohol consumption

				5) Clinical records: taking <95% of supply		
Sarna, Council, & Pujari (2008) [129]	1) Socioeconomic 2) Patient 3) Therapy 4) Condition	AACTG, BDI	AACTG	Low MA=<90%	Low: 6.6%	Factors associated with MNA: - ↓ university education - Being unemployed (OR=2.35; 95% CI: 1.22-4.88, p<0.05) - Obtaining free treatment (OR=5.71; 95% CI: 2.94-11.10, p<0.001) - Severe depression (OR=6.49; 95% CI: 2.89-14.59, p<0.001) - Baseline CD4 count>200/ml (OR=4.04; 95% CI: 1.85–8.79; p<0.001) - Hospitalization >2 times (OR=1.38; 95% CI: 1.43–11.21; p<0.01) - Moderate to severe side-effects (OR=5.40; 95% CI: 2.47-11.81; p<0.001) - Taking ≥4 medicines (OR=3.21; 95% CI: 1.44–7.12; p<0.01) Reasons for MNA: - Being busy with other things - Forget - Being away from home - Running out of pills
Schneider et al. (2004) [130]	1) Socioeconomic 2) Patient 3) Therapy 4) Health-care and system	Questionaire developed	Questionaire developed	Perfect MA=100 (0-100)	Mean MA=87	Factors associated with ↑ MA: - Better physical health (r=0.12, p<0.01) - Better mental health (r=0.20, p<0.0001) - Older ages (r=0.15, p<0.001) - Men (88.2 vs. 82.1, p<0.001) - Belief that ART was important (ORs from 1.73 to 2.24, p<0.05) - HIV-specific information (OR=1.09, p<0.05) - Overall physician satisfaction (OR=1.14, p<0.01)

						- Willingness to recommend (OR=1.09, p<0.01) - Trust (OR=1.10, p<0.05), - MA dialogue (OR=1.20, p<0.0001)
Schönnesson et al. (2007) [131]	1) Socioeconomic 2) Patient 3) Therapy	Questionnaire	AACTG	Suboptimally MA: <100%	Suboptimal dose=12% Suboptimal schedule=34% Suboptimal dietary instructions= 58%	Factors associated with ↑ MA: - Strong beliefs about future HIV health concerns (OR=2.74; 95% CI: 1.01–6.83) - Strong beliefs about ART benefits (OR=2.38; 95% CI: 1.04–5.46) - Older age (OR=0.44; 95% CI: 0.23–.83) - Stable relationship (OR=0.52, 95% CI: 0.28–.98)
Semvua et al. (2017) [132]	1) Socioeconomic 2) Patient 3) Therapy	AACTG	1) PDR 2) Patients' report on doses taken in past 4 days	MNA: PDR<95% in past two years	PDR= 42% 4-day report= 10%	Reasons for MNA: - Traveling away from home (21.5%) - Forgetfulness (34.2%) - Running out of pills (15.4%) - Busy working for survival (15.8%) Factors associated with MNA: - Younger age (OR=0.54, 95% CI: 0.36-0.80, p<0.01) - Unemployment (OR=2.89, 95% CI: 1.21-6.86, p<0.05)
Shigdel, Klouman, Bhandari, & Ahmed (2014) [133]	1) Socioeconomic 2) Patient 3) Therapy 4) Condition	Questionnaire developed	Patients' report on 7 day recall dose MA	MNA: <95%	MNA=13.3%	Reasons of MNA: - Forgetfulness (80%) - Busy schedule (19%) - Being too sick (11%) Factors associated with MNA: - Age (OR 1.04; 95% CI: 1.00–1.09) - Travel time to ART centers (OR 1.38; 95% CI: 1.12–1.71) - History of illegal drug use (OR 3.98; 95% CI: 1.71–9.24) - Adverse effects (OR 4.88; 95% CI: 1.09–21.8) Facilitators of MA:

						- Use of reminder tools (OR 3.45; 95% CI: 1.33–8.91)
Suleiman & Momo (2016) [134]	1) Socioeconomic 2) Patient 3) Therapy 4) Condition	AACTG	Patients' report of 14 days recall of intake doses	MNA: <95%	MNA= 26.6%	Reasons of MNA: - Forgetfulness (24.5%) - Too busy with other things (7.2%) - Felt better (4.7%) - To avoid side effects (5.5%) Factors associated with MNA: - Sex - Age - Marital status - Level of education - Occupation - Depression - HIV/ART related knowledge - cART regimen - Therapy duration
Sullivan et al. (2007) [135]	1) Socioeconomic 2) Patient 3) Therapy 4) Condition 5) Health-care and system	Interview questions	Interview questions	MNA: <95%	MNA=16%	Reasons for MNA: - Forgetfulness (32%) - Side effects (16%) - Inability to get to the clinic or doctor for prescription (11%) - Inability to fit medications into schedule (9%) Factors associated with MNA: - Black non-Hispanic & Hispanic respondents - Aged 18–29 or 30–39 years - Using alcohol or crack cocaine in past 12 months - Prescribed $4 medications at time of interview - Currently living in a shelter or on the street
Suryana, Suharsono, &	1) Socioeconomic 2) Patient 3) Therapy	Interview questions	Pill count	Low MA: <95%	Low MA=15.8%	Factors associated with MNA: - Employment status/occupation ($p<0.05$)

Antara (2019) [136]	4) Condition					- Type of ARV (due to adverse effect) ($p<0.01$) - Family support ($p<0.001$) Reasons for MNA: - Feeling healthy (5.94%) - Adverse effects of ARV (4.46%) - Busy (2.48%) - Far from home (1.48%)
Tessema et al. (2010) [137]	1) Patient 2) Therapy 3) Condition	Questionnaire developed	Patients' report on forgetting dose the day before	MA: never forget doses	MNA= 17.3%	Reasons for MNA: - Side effects (31.0%) - Other health problems (21.8%) Factors associated with MNA: - Treatment adverse effects (OR=1.4; 95% CI: 0.8-2.5) - Nonreadiness to HAART (OR=8.9; 95% CI: 4.8-16.7) - Contact with psychiatric care service (OR=2.2; 95% CI: 1.1-4.5) - Having no goal (OR=3.5; 95% CI: 1.1-10.8)
Tiyou et al. (2010) [138]	1) Socioeconomic 2) Patient 3) Therapy	Pre-tested questionnaire	Pre-tested questionnaire	MA: ≥95%	MNA=27.6%	Reasons for MNA: - Running out of medication (27.3%) - Being away from home (21.2%) - Being busy with other things (21.2%) Factors associated with ↑ MA: - Family support (AOR=2.12; 95% CI: 1.25-3.59)
Tyer-Viola et al. (2014) [139]	1) Socioeconomic 2) Patient 3) Therapy 4) Condition 5) Health-care and system	CESD, PSS, HCPE, ASE, SCS, RSE, SOC	VAS scale	MA: 100% in past 3 or 30 days	NR	Factors associated with MNA: - Younger ages - Not having children - Not engaging with healthcare provider - ↑ depression - Perceived stigma - ↓ self-efficacy - Self-compassion - Sense of coherence - Self-esteem

Van Servellen & Lombardi (2005) [140]	1) Patient 2) Condition 3) Health-care and system	MOS-SSS, CESD, various questions on HIV knowledge, patient-provider relationship	AACTG	MNA: <90% in past 4 days	NR	Factors associated with MNA: - Poor quality of physician-patient relationship - Greater emotional or informational support (OR=1.04, 95% CI: 1.01-1.08)
Wang & Wu (2007) [141]	1) Patient 2) Therapy 3) Condition 4) Health-care and system	AACTG	Pill count	MNA: <95%	MNA=18.2%	Reasons for MNA: - Forgetfulness (48%) - Too busy with work (31.6%) - Intolerable side effects (27.6%) Factors associated with MA: - Correct knowledge of side effects (AOR=12.85; 95% CI: 4.65-35.33; p<0.01) - Correct knowledge that MNA leads to treatment failure (AOR=5.59; 95% CI: 2.48-12.57; p<0.01) - Perceived effectiveness of treatment (AOR=5.18; 95% CI: 1.91-14.05; p<0.01) - Reminder tools (AOR=4.22; 95% CI: 1.90-9.39; p<0.01) - Perceived taking medication as no burden to daily lives (AOR=3.20; 95% CI: 1.41-7.26; p<0.01) - Doctor explains regimen each time ART is dispensed (AOR=2.35; 95% CI: 1.05-5.06; p<0.05) - Regular home visits by health care staff (AOR=2.93; 95% CI: 1.33-6.49; p<0.01) - Patients' trust in doctors (AOR=4.93; 95% CI: 1.17-20.86; p<0.05)
Watt et al. (2010) [142]	1) Socioeconomic 2) Patient 3) Therapy 4) Health-care and system	Adapted scales and questions, MOS	1) 4-day recall from AACTG 2) Modified 1-month VAS scale	Poor MA: <95%	Poor MA=5.9%	Reasons for MNA: - Forgetfulness (45%) - Being out of the house or traveling (20%) - Running out of pills (9%) - Illness or side effects" (8%)

						- Oversleeping (5%) Factors associated with MNA: - Younger ages (19-30; OR=4.03) or old (50+; OR=6.68) - ↓ perceived quality of patient-provider interaction (OR=2.75) - Ever missing clinic appointment (OR=3.13)
Wolf et al. (2007) [143]	Condition	Questions on HIV knowledge, PMAQ, REALM	PMAQ	MA: 100% in past 4 days	MNA= 52.5%	Factors associated with MNA: - ↓ literacy level
Yathiraj et al. (2016) [145]	1) Socioeconomic 2) Patient 3) Therapy 4) Condition 5) Health-care and system	Pre-tested questionnaire	Patients' 30 day recall dose MA	Low MA: <95%	Low MA=29.6%	Factors associated with ↑ MA: - Ages over 40 (OR=0.8, 95% CI: 0.5-1.3) - Females (OR=0.5, 95% CI: 0.3-0.8) - Not forgetting to take ART (OR=9.0, 95% CI: 5.1-15.0) - Not consuming alcohol (OR=3.7, 95% CI: 2.1-6.0) - Good family care (OR=3.0, 95% CI: 1.2-5.2) - Absence of opportunistic infection (OR=2.6, 95% CI: 1.2-5.6) - Sense of feeling better after taking ART (OR=0.6, 95% CI: 0.4-0.1) - Travelling >25 km to get ART (OR=0.4, 95% CI: 0.3-0.7)
Yu et al. (2018) [146]	1) Socioeconomic 2) Therapy 3) Condition	PHQ-9, GAD-7, Knowledge of ART questionnaire, question on satisfaction with medical services	CPCRA	Good MA: MA≥95%	Poor MA: 14.5%	Factors associated with MNA: - Positive depression (OR=5.95, 95% CI: 2.34–15.11) - No disclosure of HIV status to others (OR=2.62, 95% CI: 1.06–6.50)
Hypertension[3] (*n*=35)						
Al-Ramahi, (2015) [147]	1) Socioeconomic 2) Condition 3) Therapy 4) Patient	Questionnaire developed, MMAS-8	MMAS-8	MMAS - 8=high MA - 6-7=medium - <6=low	High=16.9% Medium=28.9% Poor=54.2%	1) Sociodemographic & clinical characteristics - Younger age - Living in village or camp

						- ↓ income - ↑ number of antihypertensive tablets daily/↑ dosing frequency - Evaluating health status as very good, good or poor - Having no other chronic disease 2) Side effects & reasons - Forgetfulness (61.1%) - Dissatisfaction with treatment (10.0%) - Adverse effect (10.0%) - Fear of getting used to medication (7.3%)
Bae et al., (2016) [149]	1) Socioeconomic 2) Patient	BMQ, MASES	Six yes/no questions	1)MA: "no" to all 6 questions 2) Unintentional MNA: "no" to all 3 intentional items & yes to any unintentional item 3) Intentional MNA: "yes" to any of the 3 intentional items	MA=45.6% Unintentional MNA=26.7% Intentional MNA=27.9%	1) Sociodemographic characteristics - ↑ household income 2) Medication beliefs & self-efficacy - Necessity scores ↑ in MA group (M=17.0 (SD=4.1)) than intentional MNA group (M=15.3 (SD=3.6)) - Both MNA groups ↓ self-efficacy than MA group
Barreto, Reiners, & Marcon (2014) [150]	1) Socioeconomic 2) Condition 3) Therapy 4) Health-care & system	MRCI, satisfaction with healthcare service, knowledge about disease questions	MAQ-Q	MA: taken prescribed pills 80%-120%	MNA=42.7%	Factors associated with MNA: - Little knowledge about disease - Complex drug therapy - Dissatisfaction with healthcare service
Boima et al., (2015) [151]	1) Socioeconomic 2) Condition 3) Therapy	BMQ, PHQ-9, questionnaire assessing knowledge on hypertension	MMAS-8	MNA:<8	MNA=66.7%	1) Sociodemographic & clinical characteristics - Younger age (M=54.4 (SD=13.2) - Formal education (70.9%) - Having health insurance (73.1) - Using herbal preparation for treatment (80.6%) - Depression (r=−0.21) 2) Treatment beliefs

						- Negatively related with concerns about medication (r=−0.04) - Positively with hypertension knowledge (r=0.14)
Braverman & Dedier (2009) [152]	1) Socioeconomic 2) Patient	Self-efficacy measure, physician support item, family support item	1) MEMS 2) MMAS	MEMS: average % of prescribed doses & days	MNA=28.4% (MEMS)	1) Sociodemographic characteristics - Females ↓ high school education → ↓ MA (39%) - Males with ↑ education (28%) → ↓ MA - Females who lived with someone else (35%)→ ↓ MA - Males who lived alone →↓ MA (31%)
Choi et al. (2018) [153]	1) Socioeconomic 2) Condition	Structured questionnaires (NR)	Pill counts	Poor MA: Pills taken <80%/not attending follow-up appointment	Poor MA=18.3%	1) Sociodemographics associated with good MA: - Aged ≥65 (OR=1.83; 95% CI: 1.18–2.83) - Treated at a metropolitan-located hospital (OR=1.86; 95% CI: 0.78–2.36) - Exercised 1–2 times (OR=1.43; 95% CI: 1.02–2.01) or ≥3 times (OR=1.57; 95% CI: 1.12–2.20) per week 2) Clinical factors associated with good MA: - Family history of hypertension (OR=1.72; 95% CI: 1.29–2.30) - Treatment with 2 classes (OR=1.55; 95% CI: 1.14–2.12) & ≥3 classes of antihypertensive medication (OR=3.82; 95% CI: 2.06–7.10) - Concomitant treatment for diabetes (OR=1.67; 95% CI: 1.16–2.40) or dyslipidemia (OR=1.48; 95% CI: 1.12–1.97) - Habit of low salt intake (OR=-0.64; 95% CI: -0.48–0.67)

de Terline et al. (2019) (192)	1) Socioeconomic 2) Condition 3) Therapy	MMAS-8, Sociodemographics	MMAS-8	MMAS: - 8= high MA - 6-7=medium - <6=low MA	Low=30.8% Medium=33.6% High=35.6%	Barriers to MA: - ↓ wealth index (OR=1.83; 95%CI: 1.38–2.45) - Use of traditional medicine (OR=2.22; 95%CI: 1.78–2.78) - Prescription of calcium channel blocker → ↑ MA (OR=0.8 95%CI: 0.65–0.99)
Espeche et al. (2020) (191)	1) Socioeconomic 2) Condition 3) Therapy 4) Patient	MMAS-8, Sociodemographics	MMAS-8	MMAS: - 8= high MA - 6-7=medium - <6=low MA	Low=14.3% Medium=29.6% High=56.1%	Factors associated with MNA: - Female gender (OR=1.32; 95% CI: 1.04-1.67) - ↓ education level (OR=3.55; 95% CI: 2.76-4.57) - Being under diuretic treatment (OR=0.60; 95% CI: 0.45-0.80) - Smoking (OR=0.61; 95% CI: 0.41-0.91)
Hassanein (2020) (190)	1) Socioeconomic 2) Condition 3) Therapy 4) Patient	MMAS-8, Sociodemographics	MMAS-8	MMAS: - 8= high MA - 6-7=medium - <6=low MA	Low=32.6% Medium=26.2% High=41.3%	Factors associated with MNA: - Female gender - ↓ education level - Twice-daily dose combinations - Long hypertension history - Unemployed
Holt et al. (2013) [157]	1) Socioeconomic 2) Condition 3) Health-care & system 4) Patient	CCI, GHAA scales, MGH-SFQ, CESD, RANDMOS-SS, JHAC, PSS	MMAS-8	Low MA: MMAS-8≤6	Low MA: 15% women & 13.1% men	↓ MA in men associated with: - ↓ sexual functioning (OR=2.03, 95% CI=1.31–3.16) ↓ MA in women associated with: - Dissatisfaction with communication with healthcare provider (OR=1.75, 95% CI=1.16–2.65) - Depressive symptoms (OR=2.29, 95% CI=1.55–3.38)
Jarab et al. (2018) [158]	1) Condition 2) Therapy 3) Patient	EQ-5D	MMAS-4	MNA: MMAS≥1	MNA=81%	- ↑ prescribed medications (OR=0.35, CI=0.17-1.19) - Presence of comorbid illness (OR=0.32, CI=0.15–1.02)

						- Concerns about side effects (OR=0.17, CI=0.09–0.95) - Poor HRQoL (OR=0.13, CI=0.04–0.87)
Jokisalo et al. (2002) [159]	1) Socioeconomic 2) Therapy 3) Health-care & system 4) Patient	45-item questionnaire	Questions on modification of dosage instructions & self-reported MA	MNA: taken medication less often during last year	MNA= 14% males & 13% females	1) ↓ education (OR=0.50; 95% CI:0.26-0.98) 2) ↑ perceived health care system-related problems (24%; 4 times more likely to be MNA) 3) ↑ patient problems (21%; 2 times more likely to be MNA) 4) Experiencing adverse drug effects (17%)
Karakurt & Kaşikçi (2012) [160]	1) Socioeconomic 2) Patient 3) Health-care & system 4) Condition	Questionnaire developed	Questionnaire developed	MNA: not using medication as prescribed	MNA=57.9%	1) Sociodemographic characteristics - Younger patients (χ^2=20.64) - Unaware of complications (χ^2=19.95) 2) Reasons for MNA - Forgetfulness /aloneness /negligence (49.3%) - ↑ cost (26.5%) - Old age/inactivity (16.3%)
Khadoura et al. (2020) [161]	1) Socioeconomic 2) Condition 3) Therapy 4) Patient	BMQ, TSRQ, PDRQ	MMAS-8	MNA: MMAS≥1	MNA=65.8%	Factors associated with MNA: - Younger ages (OR=1.03; 95% CI: 1.01–1.06) - Illiterate education level (OR=1.7; 95% CI: 1.08-2.67) - ↑ number of medications (OR=2.27; 95% CI: 1.91-2.71) - ↑ number of years since diagnosis (OR=1.88; 95% CI: 1.04–3.37) - ↓ self-efficacy (OR=4.47; 95% CI: 3.28–6.09) - Poor social support (OR=2.87; 95% CI: 2.66–3.09)

Khan, Shah, & Hameed (2014) [162]	1) Socioeconomic 2) Patient	MMAS-4	MMAS-4	MMAS-4 score: - 3-4=MA - 0-2=MNA	MNA=21%	1) Sociodemographic characteristics - Aged 18-30 (MNA=26.6%) 2) Reasons for MNA a. Intentional (69%) - Fear of side-effects (25.4%) - Inconvenience of taking medicines outside home (17%) - Fear of ingesting medicines (10.1%) b. Non-intentional (31%) - Forgetfulness (22.4%) - Unavailability of nearby pharmacy (4.6%)
Kretchy et al. (2013) [163]	Socioeconomic	SPS, DUREL	MMAS-8	MMAS-8 -High=8 -Poor= <8	Poor=93.3%	↑ spirituality → 2.68 times more likely to be poorly MA
Lee et al. (2013) [164]	1) Socioeconomic 2) Condition 3) Health-care & system	LHID medical facilities	MPR (% time a patient had medication available to them)	MPR: low (<50%), medium (50–79%), high MA (80%).	52.9% high MA, 25.5% medium, 21.6% low MA	1) Sociodemographic characteristics - Female gender (OR: 0.92; 95% CI: 0.89–0.95) - Ages 55–64 (OR: 0.67; 95% CI: 0.63–0.71) - ↑ socioeconomic status & treatment provided at a cardiovascular medical centre (OR=0.91; 95% CI: 0.86–0.96) - Comorbidity scores > 2 associated with ↑ MA (OR: 1.18; 95% CI: 1.08–1.28) 2) Institutional factors associated with ↑ MA - ↓ treated at medical centres & corporate institutions (OR: 0.89; 95% CI: 0.84–0.93). - Treated at institutions in rural areas (OR: 0.89; 95% CI: 0.83–0.94)
Lehane & McCarthy (2007) [165]	1) Socioeconomic 2) Condition 3) Therapy	HBM Hypertension Scale, MTQ	MARS	MARS: ↑ score → ↑ MA (scale 1-5)	M=4.75 (SD=0.52)	No statistically significant associations

Lewis, Schoenthaler, & Ogedegbe (2012) [166]	1) Socioeconomic 2) Health-care & system 3) Patient	MOS-SSS, PCM, MASES, PDI, PHQ-9 CCI	MMAS-4	MMAS: ↑ score → ↑ MNA	MNA=54.9%	- Patient-level factors predicting MA: age (β=-0.02), self-efficacy (β=-0.98), depression (β=0.04)
Li et al. (2012) [167]	1) Socioeconomic 2) Condition	PSSD, PSG, PBWN, SSG,	MMAS-8	MA: MMAS ≥80%	MNA=47.5%	1) Cultural factors - ↓ susceptibility to specific diseases (OR=1.15, 95% CI: 1.01–1.31) 2) Clinical factors - Longer length of HTN diagnosis (OR=1.06, 95% CI: 1.01–1.12)
Lowry et al. (2005) [168]	1) Socioeconomic 2) Condition 3) Therapy	Self-report questionnaire	MMAS-4	MNA: MMAS ≥1	Unintentional MNA=31% Intentional=9%	1) Sociodemographic characteristics - Non-white → ↑ MNA - <10th-grade education→ unintentional MNAs 2) Adverse effects & clinical characteristics - Intentional MNAs→ ≥5 adverse effects & less likely to have diabetes - Intentional or unintentional MNAs → increased urination & wheezing - Unintentionally MNA → dizziness & rapid pulse
Lulebo et al. (2015) [169]	1) Socioeconomic 2) Condition 3) Therapy 4) Health-care & system 5) Patient	Developed questionnaire	MMAS-4	MNA: MMAS≥1	MNA=54.2%	1) Condition variables - Uncontrolled blood pressure (OR=2.0; 95 % CI 1.1–3.9) 2) Therapy variables - Prior experience of medication side effects (OR=2.2; 95 % CI 1.4–3.3) - Taking non-prescribed medications (OR=2.2; 95 % CI 1.2–3.8) 3) Patient variables - Poor knowledge about complications of hypertension (OR=2.4; 95% CI:1.4–4.4) 4) Healthcare team & system-related variables

						- Unavailability of antihypertensive drugs in healthcare facilities (OR=2.8; 95 % CI 1.4–5.5) - Lack of education in healthcare facilities (OR=1.7; 95 % CI 1.1–2.7)
Mamaghani et al. (2020) [170]	1) Socioeconomic 2) Condition 3) Therapy 4) Patient	7-items barriers scale	MMAS-8	MMAS: - 8= high MA - 6-7=medium - <6=low MA	Low=18.2% Medium=43.6% High=38.2%	Factors associated with MNA: - Gender - Younger ages - ↓ educational level - ↓ monthly household income - ↓ hypertension duration - ↑ number of medications Reasons for MNA: - Medication cost - Nobody to help me tracking medications - Taking them when feel discomfort
Martin et al. (2010) [171]	1) Socioeconomic 2) Therapy 3) Health-care & system 4) Patient 5) Condition	Questions on provider-patient relationship, barriers to MA, CESD	Medication taking questions	MA: never took less medication than prescribed	MNA=60.1%	1) Sociodemographic & clinical characteristics - ↑ depression levels 2) Reasons for MA - Taking medication same time every day (41%) - Not having medication when take dose (36%) - Running out of medicine (35%) - Bothered by side effects (29%) - Change in daily routine (27%) 3) Provider-patient relationship - ↑ discomfort asking providers questions (74%) - ↑ likely to feel health care appointments were stressful (25%)
Náfrádi et al. (2016) [173]	1) Socioeconomic 2) Therapy 3) Patient	BMQ, MASES, accepting treatment advice scale	MARS	1) Complete MA: 100% 2) Occasional MNA: <100%	Complete intentional MNA= 53%	1) Sociodemographic characteristics - Occasional unintentional MNAs younger than completely MA (t=-2.97)

					Occasional intentional=47 % Complete unintentional= 45% Occasional unintentional= 55%	2) Unintentional MNAs: ↑ side effects than MA (t=-3.54) 3) Intentional MNAs: - ↓ self-efficacy (t=-4.54) - ↑ medication concern beliefs (t=2.13) - ↓ accepted treatment recommendations (t=2.29) 4) Unintentional MNAs: - ↓ MA self-efficacy (t=-3.15) - ↑medication concern beliefs (t=-2.96) - ↓ acceptance of treatment recommendations (t=-1.95)
Nair et al. (2011) [174]	Patient	Authors' questions	Pharmacy claims	MNA: MPR< 80%	39% MNAs	Barriers to MA - Forgetfulness (i.e., too busy, travelling & forgot to pack medication) - Not being able to make it to the pharmacy - Other reasons (e.g., change in routine, falling asleep)
Oluwole et al. (2019) (189)	1) Socioeconomic 2) Patient	TQSM	MMAS-8	MMAS: - 0= high MA - 1-4=moderate - >4=low MA	Low=9.8% Moderate=89.2 % High=1.0%	- ↓ treatment satisfaction → ↓ MA
Palanisamy & Sumathy (2009) [178]	1) Socioeconomic 2) Therapy 3) Patient	MMAS	MMAS	MNA: MMAS≥1	Baseline=100% Second interview =51.2% Final interview = 4.6%	1) Intentional reasons - Side effects (74%) - Medications not effective (40%) - Fasting once per month (40%) 2) Unintentional reasons - Forgetfulness (72%) - Medication too expensive (19%)
Park et al. (2008) [179]	1) Socioeconomic 2) Condition 3) Therapy 4) Health-care & system	Pharmacy claims	CMA based on pharmacy claims	CMA > 80%: "Appropriate MA"	MNA=17.9%	1) Predisposing factors - Females (OR=0.93, 95% CI:0.93–0.94) - Younger age & age>70 (OR=0.87 95%:0.85–0.88)

						- Neuropsychiatric diseases (OR=0.95, 95% CI: 0.92–0.98) - Medication duration: 6–12 months (OR=0.49, 95% CI: 0.48–0.50) 2) Enabling factors - ↓ monthly contributions - Rural residential area (OR=0.77, 95% CI: 0.76–0.78) 3) Modifying factors - Increase of prescribing physicians - Decrease of prescription days per visit
Rajpura & Nayak (2014a) [180]	1) Condition 2) Therapy 3) Patient	BMQ, B-IPQ, PRISM	MMAS-4	MMAS - High MA=0 - Medium= 1-2 - Low=3-4	High MA=18.8% Medium=47% Low=34.2%	1) Illness perception - ↑ threatening view of illness → ↑ MA (r=0.33) 2) Medication beliefs - Strong concerns about medications → ↓ MA (r=-0.23) - Strong beliefs that medications are necessary → ↑ MA (r=0.25) - Strong beliefs that medications are harmful → ↓ MA (r=-0.04) - Strong beliefs that physicians overprescribe medications & fear of medication overuse→ ↓ MA (r=-0.03) 3) Illness burden - Greater SIS (r=0.42) & ↓ IPM (r=-0.44) → ↑ MA
Rajpura & Nayak (2014b) [181]	1) Condition 2) Patient	BMQ, B-IPQ	MMAS-4	MNA: MMAS= 0-2	MNA=66.1%	1) ↑ favorable perceptions of illness → ↑ MA (r=0.33) 2) Medication beliefs - Stronger concerns about medication → ↓ MA (r=-0.23) - ↑ necessity of medication → ↑ MA (r=0.25) - Stronger beliefs about medication overuse → ↓ MA (r=-0.34)

Ruppar, Dobbels, & De Geest (2012) [183]	1) Socioeconomic 2) Patient	BMQ	MEMS	MA: ≥85%	MNA=48.5%	1) Sociodemographic characteristics - Education beyond high school → ↑ MA 2) Medication beliefs - ↑ concerns about medications → ↑ MNA - Stronger belief in necessity of medications → ↑ MA
Saounatsou et al. (2001) [184]	1) Socioeconomic 2) Therapy	Developed questionnaire	1) 5-point scale ranging from MNA (1) to full MA (5) 2) Number of pills forgot to take	MNA: taking ≤ 20 pills during 30 days	Mean MA: - IG=4.85 - CG=4.25	- Years of schooling positively related to MA (rs=0.33) - Duration of therapy negatively related with MA (rs=-0.45)
Stavropoulou (2012) [185]	1) Socioeconomic 2) Therapy 3) Patient	Developed questionnaire	MMAS-4	MNA: MMAS≥2	MNA=26%	1) Sociodemographic characteristics associated with ↑ MA - Older age (b=-0.02) - ↑ education (b=-0.30) 2) Factors associated with ↑ MA - ↑ education on medication (b=-0.37) - Use of media (b=-1.27) & Internet (b=-1.21) to be informed for medication
Vawter et al. (2008) [187]	1) Socioeconomic 2) Condition 3) Therapy 4) Patient 5) Health-care & system	Question on difficulty taking medication	NR	NR	Medication difficulties =28.4%	1) Sociodemographic & clinical characteristics - Younger adults (18-44 (OR=2.6; 95% CI: 1.8–3.7) & 45-54 (OR=1.8; 95% CI: 1.2–2.5)) - ↓ income (OR=1.6; 95% CI: 1.1–2.2) - Having a mental health condition (OR=1.6; 95% CI: 1.2–2.1) - Taking fewer medications - Fewer primary care visits 2) Reasons for MNA - Forgetfulness (32.4%) - Cost (22.6%) - No insurance (22.4%) - Side effects (12.5%)

Note. AACTG= Adaptation of the Adult AIDS Clinical Trials Group; AED= antiepileptic drug; AGAS= Antiretroviral General MA Scale; AOR=Adjusted Odds Ratio; APS= American Pain Society Outcome Questionnaire; aPR= Adjusted Prevalence Ratio; ARMS-D= MA to Refills & Medication Scale for Diabetes; ART= Antiretroviral Treatment; ASE= MA Self-Efficacy; ASKS-12= MA Starts with Knowledge; AUDIT-C= Alcohol Use Disorders Identification Test; B-IPQ=Brief Illness Perceptions Questionnaire; BDI= Beck Depression Inventory; BMQ=Beliefs about Medicines Questionnaire; BQT= Barriers Questionnaire-Taiwan Form; BPS= Berger Stigma Scale; CCI= Charlson Comorbidity Index; CD= Complications of Diabetes; CESD= Center for Epidemiologic Studies Depression Scale; CG= Control group; CMA= Cumulative medication MA; CP= Complexity of pharmacotherapy; CPRCA= Community Programs for Clinical Research on AIDS; DASS= Depression, Anxiety & Stress scale; DKT= diabetes knowledge test; DLC= Diabetes locus of control; DM-KS= Diabetes Mellitus Knowledge Scale; DSCAQ= Diabetes Self-Care Activities Questionnaire; DUREL=Duke Religion Index; EG= Experimental group; EQ-5D= EuroQol instrument; ESMS= Epilepsy Self-Management Scale; ET= Endocrine Therapy; FCQ= Fear of Complications Questionnaire; GAD-7= Generalized Anxiety Disorder 7-item; GHAA= Group Health Association of America Consumer Satisfaction Survey; HADS= Hospital Anxiety and Depression Scale; HAT-QoL= HIV/AIDS-Targeted Quality of Life; HBM= Health Belief Model scales; HCPE= Health Care Provider Engagement; HRQoL=health-related quality of life; HTN=Hypertension; ICS= inhaled corticosteroids; INT= Intentions to adhere to the treatment plan; IPAQ= International physical activity questionnaire; IPM= illness perception measure; IPQ-R= Illness Perception Questionnaire; JHAC=John Henry Active Coping Scale; KSS= Kilifi stigma scale; LHID= Longitudinal Health Insurance Database; LSSS= Liverpool Seizure Severity Scale; MA=Medication MA; MAQOL= Marks asthma-specific quality-of-life questionnaire MAQ-Q= Medication MNA Questionnaire; MARS=Medication MA Report Scale; MASE-R= Medication MA Self-efficacy Scale-Revision; MASES=Medication MA Self-Efficacy Scale; MCQ= Medication Compliance Questionnaire; MDKT= Michigan Diabetes Knowledge Test; MEMS= Medication Event Monitoring System; MGH-SFQ= Massachusetts General Hospital Sexual Functioning Questionnaire; MGL= Morisky-Green-Levine questionnaire; MGT= Morisky-Green Test; MHI= Mental Health Inventory; MHLCS= Multi-dimensional Health Locus of Control Scale; MMAS= Morisky Medication MA scale; MNA= Medication MNA; MOS= Medical Outcomes Study; MOS-SSS= Medical Outcomes Study Social Support Survey; MPK=Medical Prescription Knowledge; MPR= Medication Possession Ratio; MRCI= Medication Regimen Complexity Index; MSPSS= Multidimensional Scale of Perceived Social Support; MT= MedTake; MTQ= Medication-Taking Questionnaire NR=Not Reported; NEO-PI-R= Revised NEO Personality Inventory; OR=Odds Ratio; OSS-3= Oslo social support scale; PBWN=Perceived Benefits of Western Medication for HTN; PCAQ= Perceived Control of Asthma questionnaire; PCM= Provider communication measure; PDC= Proportion of days covered; PDI= Perceived Discrimination item; PHQ= Patient Health Questionnaire; PLHIV-Pro= Self-developed PLHIV profile; PMAQ= Patient Medication MA Questionnaire; PAIDQ= Problem Areas In Diabetes Questionnaire; PRISM= Pictorial Representation of Illness & Self Measure; PSG=Perceived Susceptibility in General; PSH= Physical Symptoms Checklist; PSM= Perceived Sensitivity to Medicines; PSS=Perceived Stress Scale; PSSD=Perceived Susceptibility to Specific Diseases; PU= Perceived utility of the treatment plan; QOL=Quality of Life; QOLIE-31= Quality of Life in Epilepsy; RANDMOS-SS=Medical Outcomes Study Social Support Survey; REALM= Rapid Estimate of Adult Literacy in Medicine; SB= Absence of barriers to MA; SCI= Self as Carer Inventory; SCS= Self-Compassion Scale; SDSCA-MS= Summary of Diabetes Self-Care Activities medications subscale; SES= Self-efficacy Scale; SF-12= Short Form of General Health; SF-36= Short-Form-36 Health Survey; SHCS-AQ= Swiss HIV Cohort Study MA Questionnaire; SIBS= Spiritual Involvement and Beliefs Scale; SIS= Self-Illness Separation; SMAQ= Simplified Medication MA Questionnaire; SOC= Sense of Coherence Scale; SPAS= Self-perceived asthma severity; SPS= Spiritual Perspective Scale; SSC-HIV= Sign and Symptom Checklist for Persons with HIV; SSG= Social Support in General; SWB= Spiritual Well-Being Scale; TQSM= Treatment Satisfaction Questionnaire for Medications; VAS= Visual Analog Scale; WHOQOL-BREF= WHO Quality of Life-BREF.

[1]Barriers were coded into socioeconomic-related factors, health-care team and system-related factors, condition-related, therapy-related, and patient-related factors.
[2]Only findings on barriers which were significant are reported.
[3]Studies are listed alphabetically based on condition and then by the names of the authors.

Appendix G

Table 3

Barriers of Medication Adherence (MA) and Findings of Qualitative studies (N=33)

Authors (Date)	Assessed Barriers[1]	Specific Measure(s) for barriers	Specific Measure(s) for MA	Definition/ Scoring of MA	Key Findings	
					MA	Barriers
Asthma[2] (*n*=1)						
Scherman & Löwhagen (2003) [6]	Patient	Interview questions	Interview questions	NR	NR	Three categories: - Access to medicine is important to relieve discomfort & to avoid fear - Medicine damages your body & your identity without curing illness - Production & distribution of medicine is a profit-seeking commercial undertaking
Diabetes[2] (*n*=7)						
Atinga, Yarney, & Gavu (2018) [20]	Patient	Interview questions	Interview questions	MNA: skipping doses/ discontinued medication	NR	Barriers to MA: 1) Perception of medication efficacy (e.g., low trust) 2) Recourse to herbal medicine 3) Recourse to spiritual or divine healing (e.g., prayers) 4) Interaction effect of polypharmacy practice (e.g., disorders) 5) Routine work & related busy schedules (e.g., forgetfulness caused by routine schedules) 6) Societal norms (e.g., prevailing norms of the environment) 7) Poor understanding of prescriber instructions 8) Knowledge & experience of medication
Baghikar et al., (2019) [21]	1) Socioeconomic 2) Patient 3) Health-care & system	Interview questions	Interview questions	NR	NR	1) Personal barriers - Fear/concerns about medication side effects - Utility of medication (i.e., medication not necessary) - Desire to control diabetes with lifestyle 2) Interpersonal barriers - Poor communication with providers 3) Personal Facilitators - Importance of diabetes medication 4) Interpersonal Facilitators - Discussing MA with providers

						- Family support 5) Societal Barriers - Cost
Dehdari & Dehdari (2019) [25]	1) Socioeconomic 2) Condition 3) Therapy 4) Health-care & system 5) Patient	Interview questions	Interview questions	NR	NR	Barriers to MA: 1) Medication cost 2) Treatment characteristics e.g., worry about side effects 3) Personality traits e.g., not responsible, anxiety 4) Situational influences e.g., party, travelling 5) Inadequate knowledge e.g., lack of diabetes knowledge 6) Inadequate perceived threat about diabetes e.g., not accepting diabetes as disease Medication beliefs: 1) Belief in effectiveness of treatment 2) Belief in more effectiveness of complementary therapies than medication use 3) Prioritizing use of pills instead of insulin injection
Jaam et al. (2018b) [30]	1) Socioeconomic 2) Condition 3) Therapy 4) Health-care & system 5) Patient	Interview questions	Interview questions	NR	NR	Barriers to MA: 1) Socioeconomic factors - Younger age, ↓ education, religious beliefs, working conditions 2) Patient–provider consultation - Patient-provider communication - Seeing multiple physicians/health care providers 3) Social & environmental factors - Social pressure - Traveling to visit friends & relatives 4) Patient factors - Perceptions & attitudes (e.g., inadequate knowledge, negative perceptions)
Jeragh-Alhaddad et al. (2015) [31]	1) Socioeconomic 2) Condition 3) Therapy 4) Health-care & system 5) Patient	Semi-structured interviews	Semi-structured interviews	NR	NR	1) Personal barriers - Lack of education/ awareness about diabetes/ medications - Beliefs about medicines/diabetes - Attitude toward diabetes (e.g., denial) - Perceptions of social support - Impact of illness on patient's life 2) Health care provider-related barriers - Perceptions of favoritism/inequality of care provision

						- Discontinuity of care 3) Health care system-related barriers - Unavailability of medications - Access difficulties - Lack of trust in the government health care system 4) Cultural/religious barriers - Social stigma - God-centered locus of control
Peeters et al. (2015) [39]	Patient	Interview questions	Interview questions	MA: >80% of medication	NR	Barriers & facilitators: - Forgetfulness (e.g., broken routines or problems) - Causal beliefs about stress - Non-awareness of chronic nature of diabetes - Beliefs about medication - Lack of trust in medical expertise of doctor - Concerns about taking many pills - Mental problems
Rezaei et al. (2019) [42]	1) Socioeconomic 2) Condition 3) Therapy 4) Health-care & system 5) Patient	Semi-structured interviews	Semi-structured interviews	NR	NR	Barriers to MA: 1) Lack of trust in medical knowledge - Misconceptions about diabetes - False beliefs - Ignorance 2) Lived experiences of disease - Medication side effects - Physical challenges 3) Challenges of everyday life - Mental/psychological stress - Preoccupations of everyday life 4) Interactive/economic challenges - Lack of empathy/behavioral affiliation e.g., family support - Weakness/financial dependence
HIV[2] (*n*=19)						
Balcha, Jeppsson, & Bekele (2011) [63]	1) Socioeconomic 2) Therapy 3) Health-care & system	Semi-structured interviews & focus groups	Semi-structured interviews & focus groups	NR	NR	Barriers to MA: 1) ART medications as ‘‘long-term life support” 2) Free ART as ‘‘Expensive’’ 3) Expansion of Free ART as ‘‘Sharing the New Hope’’ 4) Regular Follow-Up as ‘‘Devotion to Life-Long Crisis Management’’

Barnett et al. (2013) [64]	1) Socioeconomic 2) Condition 3) Therapy 4) Patient	Semi-structured interviews	Semi-structured interviews	NR	NR	Barriers to MA: 1) Patient-cited - Side-effects - Not using condoms - Lack of understanding around medication timing - Time delay between medication and food intake - Large pill size 2) Key-informant-cited - Patient drinking - Non-disclosure - Pill fatigue - Forgetfulness
Bezabhe et al. (2014) [66]	1) Socioeconomic 2) Condition 3) Therapy 4) Health-care & system 5) Patient	Semi-structured interview & focus groups questions	Semi-structured interview & focus groups questions	NR	NR	1) Patient-Related Factors - Economic constraints, disclosure of HIV status, social support, use of reminder tools, stigma and discrimination, responsibility to raise children 2) Healthcare-Related Factors - Patient education and counseling facilitated MA while business of healthcare providers, poor laboratory service, and poor medical record handling impaired MA and retention
Curioso et al. (2010) [70]	1) Socioeconomic 2) Condition 3) Therapy 4) Health-care & system 5) Patient	Semi-structured interviews	Semi-structured interviews	NR	NR	Facilitators of MA: - Patient characteristics: positive results, self-efficacy - Medication beliefs: beliefs in drugs efficacy, faith in treatment, understanding the need for compliance - Daily schedules: having fixed routine, use of reminder tools - Interpersonal relationships: family reminding - Other: positive & open relationships with medical providers Barriers to MA: - Patient characteristics: simply forgot, fear of disclosure/stigma, financial constraints - Medication beliefs: side effects, harmful, unconvinced of efficacy - Daily schedules: dietary requirements difficult to balance, being away from home, too busy - Other: lack trust in medical provider, feeling healthy, feeling hopeless, ART caused unwanted changes to body

Edwards (2006) [74]	1) Socioeconomic 2) Condition 3) Patient	Journals & semi-structured interviews	Journals & semi-structured interviews	NR	NR	Barriers to MA: - HIV/AIDS-related stigma - Feeling unloved and uncared for - Relationship turbulence - Being married to an HIV-positive partner Facilitators of MA: - Having a supportive family - Presence of young children in their lives
Holtzman et al. (2015) [83]	1) Socioeconomic 2) Condition 3) Therapy 4) Health-care & system 5) Patient	Semi-structured interviews	Semi-structured interviews	NR	NR	Barriers to MA: 1) Patient factors - Predisposing: stigma, mental illness, health literacy - Enabling: social support, forgetfulness, reminder strategies, medication characteristics, insurance, housing - Perceived need: taking medication when sick 2) Health Care Environment - System: pharmacy services, unprofessional staff, refills not ready as promised, limited hours - Clinic: appointment scheduling, clinic experiences - Provider: trust, compassion, delivery of individualized care, responsiveness 3) External environment - Competing life activities e.g., jobs, schooling, caregiving responsibilities for children and the elderly, legal issues
Konkle-Parker, Erlen, & Dubbert (2008) [88]	1) Socioeconomic 2) Condition 3) Therapy 4) Health-care & system 5) Patient	Focus groups	Focus groups	NR	NR	Barriers to MA: 1) Patient-related - Perceived burden of extra planning, denial of HIV diagnosis, life stress 2) Regimen-related - Difficult characteristics of medicines e.g., side effects, number & size of pills 3) Environment-related - Social stigma & shame e.g., social rejection, loss of social relationships Facilitators of MA: 1) Patient-related - Acceptance of diagnosis, thinking about consequences of not taking medicines, prayer and spirituality 2) Regimen-related

						- Improvements in medicines e.g., use of combination pills - Fewer dietary restrictions - Strategies used to reduce side effects 3) Environment-related - Support from family and friends 4) Provider-related - Support from healthcare providers
Krummenacher et al. (2014) [90]	1) Socioeconomic 2) Patient 3) Therapy 4) Condition 5) Health-care and system	Interview questions	Patients' report	MNA: MA≤90%	MNA= 16.2%	Barriers to MA: 1) Cognitive, emotional and motivational factors - Perceptions/representations e.g., perception of treatment - Psycho-emotional & motivational factors e.g., clinical data - Cognitive factors e.g., memory - Physical status e.g., energy/well-being - Religion 2) Environmental, organisational and social factors - Routine - Interferences - Relationship with healthcare providers - Interpersonal relationships e.g. social support - Other factors e.g., money, drug addiction 3) Treatment and disease factors - Medications e.g., effects, co-medication, complexity Facilitators of MA: 1) Cognitive, emotional and motivational factors - Perceptions/representations e.g., acceptance of disease - Psycho-emotional & motivational factors e.g., having goals - Religious beliefs 2) Environmental, organisational and social factors - Routine e.g., associated with daily routine, reminders - Interpersonal relationships e.g. living with someone - Good relationship with healthcare providers 3) Treatment and disease factors - Medications e.g., no symptoms/decrease in side effects
Kumarasamy et al. (2005) [91]	1) Socioeconomic 2) Condition 3) Therapy 4) Health-care & system	Interviews	Interviews	NR	NR	Barriers to MA: - Cost - Lack of social support, fears about stigma, & privacy concerns - Perceived benefits of MNA

	5) Patient					Facilitators of MA: - Social support systems - Perceived MA benefits (better overall health, living longer) - Perceived consequences of MNA (decreased quality of life)
Murphy et al. (2000) [101]	1) Socioeconomic 2) Condition 3) Therapy 4) Health-care & system 5) Patient	Focus groups & questionnaire	Report how closely followed schedule over past 7 days	NR	Fully MA=33% Most of time= 40% Half of time= 19% Only a little=8%	Barriers to MA: - Slept through dose time - Had problems taking pills with special instructions - Had change in daily routine - Did not have medications with me - Busy and did not want to stop to take medications - Simply forgot - Felt depressed or overwhelmed - Felt angry, depressed, or hopeless that I had to deal with this - Wanted to forget the whole thing - Wanted to avoid side effects - Had too many pills to take - Beliefs regarding MA - Erratic daily schedules, travelling, or left home - Unwillingness to take doses in public places - Patient satisfaction with provider Facilitators to MA: - Belief MA would allow to live longer & healthier lives - Predictable daily schedules - Carrying medications when leaving home - Interactions with other people - Pill reminders - Being involved in initial decision-making - Changing a medication regimen that was too complicated - Routine home delivery of prescription refills
Murray et al. (2009) [102]	1) Condition 2) Patient	Interviews	Interviews	NR	NR	Factors associated with MNA: - Side effects - Get better - Fear of divorce - Not wanting to take it - Rumors from others saying the drugs are bad - Lack of food - Fear of taking drugs for life - Fear of being laughed at

Patel et al. (2012) [116]	1) Socioeconomic 2) Condition 3) Therapy 4) Health-care & system 5) Patient	Semi-structured interviews	Semi-structured interviews	NR	NR	Barriers to MA: - Long distance to center - Wait for long time in hospital - Being called again and again for medication - Fear of physical reactions - High cost Facilitators of MA: - Doctor's advice - Family members reminders - Medication would help living a longer life - ART counseling - Monitoring side effects - Poor health
Phuphanich et al. (2016) [119]	1) Patient 2) Health-care & system 3) Therapy	Semi-structured interviews	Semi-structured interviews	NR	NR	Barriers to MA: 1) Patient - Stigma of having HIV 2) Medication - Side effects - Storage (e.g., medication that needed to be refrigerated) 3) Health System - Access and affordability (e.g., cost) Facilitators to MA: 1) Patient - Illness is attributed to karma - Social support 2) Medication - Preparation (e.g., reminders, pill boxes) 3) Health System - Good communication with physicians, nurses etc.
Portelli et al. (2015) [122]	1) Socioeconomic 2) Condition 3) Therapy 4) Health-care & system 5) Patient	Semi-structured interviews	Semi-structured interviews	NR	NR	Barriers to MA: 1) Transport - Access/distance - Transport costs 2) Forgetfulness 3) Work 4) Stigma - Fear of disclosure

						- Loss of motivation and lack of social support 5) Psychological distress 6) Services 7) Use of alternative medicine Facilitators to MA: 1) Benefits of taking medication and problems if medication not taken 2) Knowledge about the importance of MA 3) Acceptance of HIV status 4) Social support 5) Reminders 6) Service provider 7) Education on HIV decreasing stigma
Rasmussen et al. (2013) [123]	1) Socioeconomic 2) Condition 3) Therapy 4) Health-care & system 5) Patient	Semi-structured interviews	Pill counts, self-report & clinic attendance	MA: 1) Pill count ≤7 pills 2) Visited clinic before prescriptions ran out	NR	Barriers to MA: - HIV-related knowledge - Treatment related costs and competing livelihood needs - Poor clinic infrastructure and perceived stigma - Traditional practices (e.g., traditional conviction) Facilitators of MA: - HIV-related knowledge (e.g., importance of taking medication at the designated hour) - Experienced treatment benefits of MA - Complementing social networks with healthcare providers
Remien et al. (2003) [124]	1) Condition 2) Therapy 3) Health-care & system 4) Patient	Interview questions	Interview questions	NR	NR	Barriers to MA: 1) Experience of Side Effects and Concerns About Toxicity 2) Role of Past and Current Substance Use 3) Regimen Demands and Planning 4) Priorities, Competing Concerns, and Mood States 5) Social Support Facilitators of MA: 1) Belief and Trust in Antiretroviral Medicine and Health Care Providers - Belief that treatment is beneficial to health and survival - Credit medication with recovery from serious illness 2) Social Support 3) Future Orientation (e.g., hope for future)

Sabin et al. (2008) [126]	1) Socioeconomic 2) Condition 3) Therapy 4) Health-care & system 5) Patient	Semi-structured interviews	Semi-structured interviews	NR	NR	Barriers to MA: - Stigma of HIV - Mental health issues e.g., anxiety, depression - Financial concerns e.g., ART-related worries, lack of money - Forgetfulness - Regimen-related problems e.g., strict timing, work demands - Side effects - Substance abuse
Sanjobo, Frich, & Fretheim (2008) [128]	1) Socioeconomic 2) Condition 3) Therapy 4) Health-care & system 5) Patient	Interviews & focus groups	Interviews & focus groups	NR	NR	Barriers to MA: 1) Patients' beliefs and behaviours - Side-effects, pill burden, beliefs about ART, forgetfulness 2) Health services-related - Lack of communication about ART between health care professionals and patients, time constraints during consultations 3) Socio-economic and cultural - Stigma and discrimination, disclosure of one's status as HIV positive, concerns about confidentiality Facilitators of MA: 1) Patients' beliefs and behaviours - Feeling better, prospects of living longer, prayers 2) Health services-related - Nutritional support, information about ART & free treatment 3) Socio-economic and cultural - Self-disclosure, support groups, free transport
Wondiye et al. (2016) [144]	1) Socioeconomic 2) Condition 3) Therapy 4) Health-care & system 5) Patient	Semi-structured interviews	Semi-structured interviews	NR	NR	1) Individual patients' beliefs and behaviors related themes - Barriers to MA: Feeling better, substance-misuse, perception about ART, simply forgetting and being busy - Facilitators of MA: MA aids, responsibilities related to family, prospects of living longer, disclosure of HIV status 2) Socio-economic and cultural related themes - Barriers to MA: Economic constraints, stigma and discrimination, barriers relating to religion and rituals, lack of support an - Facilitators of MA: Disclosure of HIV status, programs for income generation, looking someone improved with ART 3) Healthcare provision and system related themes

						- Barriers to MA: Poor clinic infrastructure and perceived stigma, fatigue of healthcare providers - Facilitators of MA: Nutritional support, counseling, education, trusting health workers 4) Drug related theme - Barriers to MA: Pill burden, size of drugs, side effects - Facilitators of MA: Improved health
Hypertension[2] (*n*=6)						
Amira & Okubadejo (2007) [148]	1) Socioeconomic 2) Patient 3) Therapy	Structured interviews	Structured interviews	MNA≥2 days	MNA= 34.2%	Reasons for MNA - 60% miscellaneous factors (e.g., felt cured) - 23.8% financial reasons - 16.2% side effects
McLane, Zyzanski, & Flocke (1995) [172]	1) Socioeconomic 2) Condition 3) Therapy 4) Health-care & system	Interviews	Interviews	MNA≥once per month	MNA= 24%	1) Sociodemographic & clinical characteristics - Private insurance - Having ≥3 other illnesses - Living with spouse or other - Family history of hypertension 2) Other factors - ↓ time spent with physician per visit - Side effects
Najimi et al. (2018) [175]	1) Socioeconomic 2) Condition 3) Therapy 4) Health-care & system 5) Patient	Semi-structured interviews	Semi-structured interviews	NR	NR	1) Lifestyle challenges - Economic problems - Life responsibilities - Lack of family cooperation 2) Patient incompatibility - Depression - Patient's fatigue from the process of MA - Dissatisfaction with medication - Inability to tolerate the treatment 3) Forgetting of medicine use - At the start of the diagnosis 4) Non-expert advice - Negative recommendations & experiences from the patient's companions
Ogedegbe et al. (2004) [176]	1) Condition 2) Therapy	3 interview questions	Interview questions	NR	NR	1) Patient-specific barriers - Forgetfulness

	3) Health-care & system 4) Patient					- Beliefs (addiction to antihypertensives, medications are undesirable) - Attitudes (denial negligence, dislike for pills) 2) Medication-specific barriers - Side effects - Treatment duration - Dosing frequency - Quality of pills 3) Disease-specific barriers - Symptoms (absence vs. having symptoms) - Manifestation (feeling well or not feeling ill) 4) Logistic barriers - Access (not having medications, location) - Inconvenience (carrying medications, frequent clinic visits)
Rimando (2013) [182]	1) Socioeconomic 2) Condition 3) Therapy 4) Health-care & system 5) Patient	Interview questions	Interview questions	NR	NR	1) Self-efficacy - ↓ self-efficacy & inability to make healthy behavior change 2) Patient-provider communication 3) Social support
Tsiantou et al. (2010) [186]	1) Condition 2) Therapy	Semi-structured interviews & focus groups	Semi-structured interviews & focus groups	NR	NR	1) Factors affecting MA - Previous hypertension experiences - Fear or knowledge that they could suffer from a complication - Systematic disease management - Acceptance of the disease & adoption of patient's role 2) MA characteristics - Easier if medication received in the morning - Drug substance - No longer suffering from symptoms/ believing have controlled blood pressure.

Note. MA=Medication Adherence; MNA= Medication Non-Adherence; NR= Not reported.

[1]Barriers were coded into socioeconomic-related factors, health-care team and system-related factors, condition-related, therapy-related, and patient-related factors.
[2]Studies are listed alphabetically based on condition and then by the names of the authors.

Appendix H

Table 4

Interventions of Medication MA and Findings (N=56)

Authors (Date)	Definition of MA	Type of intervention[1]	Length of Intervention	Description of intervention (IG) [2]	Control Group (CG)[2]	Key Findings
Asthma[3] (*n*=4)						
MacDonell et al. (2016) [188]	1) 6-item questionnaire: ↑ scores → poorer MA 2) Doses missed in last 7 days	Digital	3 months	1) Two CIAS-delivered sessions: Motivational Enhancement System-based + feedback on medication & readiness to improve MA 2) EMA: reminders delivered between CIAS sessions	1) CIAS-delivered asthma education (e.g., facts, myths, quizzes) 2) EMA: text-messages for asthma education (not reminders)	- Improvements in MNA at 1 & 3 months follow-up in both groups - IG: ↑ improvements in MA (1 month: d=0.27; 3 months: d=0.40) - IG: ↓ number of doses missed at 1-month (d=0.15) & 3-months (d=0.30) - No sign. differences between IG and CG
Mohan et al. (2018) [189]	MMAS-8: - High=8 - Medium=6-7 - Low<6	Digital	1 month	Medisafe app: reminders	Medication reminder card: details about order medications taken	IG: changes from baseline to post: - Low MA: 82% → 0% (Mdiff=4.02, p<0.01) - Forgetfulness: 92% → 0% - Missing doses for other reasons: 50% →12% - Symptoms under control: 68% →0% CG: - Low MA :66% → 6% (Mdiff=3.44; p<0.01) - Forgetfulness: 90% → 8% - Missing doses for other reasons: 50% →12% - Symptoms under control: 54% → 20%
Strandbygaard, Thomsen, & Backer (2010) [190]	Pill count: % of medication taken	Digital	3 months	Daily SMS reminders	No SMS reminders	IG: Increase in MA - 7.9% (week 4) → 81.5% (week 12; Mchange=3.6%; 95% CI:-8.5-15.7%) CG: Decrease in MA - 84.2% (week 4) → 70.1% (week 12; Mchange=-14.2%; 95% CI:-24.2-4.1%)

Weinstein et al. (2019) [191]	MNA: in SmartTrack MF/F<60%	Digital	3 months	AAP application: - Identifying medication barriers - Barrier-specific MI strategies	UC	IG: Mean MF/F MA: -No baseline -Week 2=88.75% -Month 1=80.70% -Month 2=77.55% -Month 3=76.80% -Overall=81.00% -Post-treatment MNA=25.00% No measurements for CG
Cancer[3] (*n*=2)						
Spoelstra et al. (2015) [192]	MA: 1) taking pills in past 7 days 2) returned texts in IG	Digital	10 weeks	Daily text message reminders	NR	-No difference between IG vs. CG (M=5.95 in both; ES=0) IG (% MA) -Week 2: 73% -Exit interview (week 10): 65% CG (% MA) -Week 2: 63% -Exit interview (week 10): 73%
Spoelstra et al. (2016) [193]	MA: 1) taking pills in past 7 days 2) pill counts during exit interview	Both	9 weeks	Daily text message reminders+UC (i.e., instructions & information on medication)	UC: instructions & information on medication	-No difference between IG & CG (IG:M=6.5; CG:M=7.2, ES=0.29) IG (% MA) -Week 1: 66% -Exit interview (week 9): 87% CG (% MA) - Week 1: 73% -Exit interview (week 9): 79%
Diabetes[3] (*n*=12)						
Arora et al. (2014) [194]	MMAS-8: ↑score= ↑MA	Digital	6 months	TexT-MED (digital)+UC (face-to-face): Educational/motivational text messages, digital medication reminders	UC	TExT-MED group: -↑ MA pre to post (4.5 →5.4) CG: -↓-0.1 (95% CI: 0.1-2.1)

Brath et al. (2013) [195]	Minor MA: <70% drugs taken	Digital	52 weeks	MON followed by CON: - MON phase: mAMS system to monitor MA, medication blisters SMS reminders - CON phase: medication blisters, routine care, medication intake diaries	CON followed by MON	- No sign. differences between groups - MON phase: 13.2% minor MA
Gatwood et al. (2016) [196]	Pharmacy claims: PDC≥80%	Digital	90 days	Daily tailored text messages: education, motivation, reinforcement and treatment-related beliefs	SC	- No sign. differences between groups from baseline to follow up (ES=0.03) - Mean PDC at baseline: IG (84.4%) vs. CG (87.1%)
George et al. (2018) [197]	MMAS-8: - High=8 - Medium =6-7 - Low<6	Face-to-Face	2 months	High MA: teach-back method patient counseling Medium MA: teach-back method, patient counseling, & patient medication information leaflet Low MA: audio-visual aids, teach-back method, patient counseling, & patient medication information leaflet	N/A	High: pre vs. post - 8.3% →13.2%: No sign. changes Medium: pre vs. post - 28.5% →33.6%: Sign. change with 18% from medium to high MA Low: pre vs. post - 63.2% →53.0%: Sign. change with 16% from low to medium MA
Huang et al. (2019) [198]	MNA: Strongly agree/agree to ASK-12 1 of 2 questions	Digital	12 weeks	Medisafe reminder	No reminders	- Baseline MA: - IG: 28.6 (SD=5.2) - CG: 27.2 (SD=5.8) - Post-treatment: - IG: M=25.5 (SD=4.4) - CG: M=28.5 (SD=7.0) - Sign. differences between groups at post-treatment → ↑ MA in IG (Mean diff.=-4.73; 95% CI: -8.26- -1.21)
Kjos, Vaughan, & Bhargava (2019) [199]	NR	Digital	6 months	Medsimple app: reminders, pharmacy locator, track changes on medication	N/A	ARMS - No sign. differences pre-post - Forget to take: ↑ MA post - Skip dose before doctor appointment: ↓ MA post

Li et al. (2020) [200]	NR	Face-to-face	4 weeks	MI-based PEP: barriers to MA, motivation enhancement, psychoeducation	Education on diabetes & medication	- Post-treatment: - IG: M=3.05 (SD=1.12) - CG: M=3.00 (SD=1.34) - No sign. differences
Melko et al. (2010) [201]	NR	Both	6 months	1) 3 face-to-face consultations: Setting goals, reinforcement of goals 2) 3 telephone calls: reinforcement	N/A	- Reduction in average number of barriers (Pre: M=3.7, SD=2.3; Post: M=2.2, SD= 1.7) - Change in % endorsement of barriers from pre to post: - Attitudes & beliefs: 70%→35% - Lifestyle: 61%→43%
Nelson et al. (2016) [202]	SDSCA-MS: <7 sub-optimal MA	Digital	3 months	MED intervention: SMS & IVR to promote MA	NR	- MA in IG improved at 1 month (AOR=3.88; 95% CI: 1.79, 10.86) & 2 months (AOR=3.76; 95% CI: 1.75, 17.44), but not at 3 months (AOR=1.49; 95% CI: 0.66, 3.10)
Owolabi et al. (2020) [203]	NR	Digital	6 months	1) SMS reminders, motivational, advice and support messages 2) SC	SC	- IG: M=6.9, CG: M=6.9 - No sign. differences between groups
Sugita et al. (2017) [204]	MMAS-8: - High=8 - Medium=6-7 - Low=<6	Digital	6 months	HL-related messages (e.g., books about diabetes, education, reinforcement) + reminders	Reminders only	IG: Pre to post changes - M=6.15 (SD=1.1) → M=6.66 (SD=1.37) CG: Pre to post changes - M=5.86 (SD=1.55) →M=6.26 (SD=1.28) - No sign. differences between groups
Vervloet et al. (2012) [205]	1. Number of days without dosing 2. % missed doses 3. % doses taken within agreed & predefined standardized time windows	Digital	6 months	RTMM medication dispenser (send SMS when medication is opened) + SMS reminders	RTMM medication dispenser	- Number of days without dosing & missed doses: no sign. differences - % of doses taken: - IG received sign. ↑ (50-81%) than CG (39-70%) - IG missed 5% sign. ↓ doses than CG

HIV[3] (*n*=26)						
Claborn (2013) [206]	AACTG: ↑ scores → ↑ MA (0-100)	Digital	1 session	1) eLS: MI & CBT techniques, problem solving 2) TAU	TAU	- Sign. differences at baseline: - IG (M=67.2, SD=34.3) vs. CG (M=80.8, SD=26.4) → ↑ MA in CG $t(92)=-2.16$, $p<0.05$ - Improved MA at follow-up in IG → no sign. results - No sign. differences over time & 1-month follow up between conditions
Da Costa et al. (2012) [207]	MA: taken doses ≥95%	Digital	4 moths	SMS reminders	No SMS messages	Self-report MA: - Baseline: IG=100% vs. CG=100% - Post-treatment: IG=100% vs. CG=84.6% Pill count MA: - Baseline: IG=75% vs. CG=69.2% - Post-treatment: IG=50% vs. CG=38.5% MEMS MA: - Baseline: IG=75% vs. CG=61.5% - Post-treatment: IG=75% vs. CG=46.2% - No sign. differences between groups
Dilorio et al. (2008) [208]	MEMS: % of doses taken	Face-to-face	3 months	MI: understanding of medication-taking behaviors and actions to successfully maintain high MA	UC	% Doses taken: - IG: Baseline=79.1%, Post-treatment=70% - CG: Baseline=80.2%, Post-treatment=65% - ↑ doses taken in IG at post-treatment vs. CG
Goujard et al. (2003) [209]	PMAQ: - 1=poor MA - 4=good MA	Face-to-face	12 months	Educational Program: planning card with stickers showing medication, session on knowledge on HIV	SC	- Sign. ↑ in MA in IG at post-treatment & ↓ in CG
Guo et al. (2018) [210]	% missed medication within last 30 days	Digital	12 weeks	1) SMS greetings and reminders 2) Articles on side effect, medication & stress management, & healthy lifestyle	Nutrition articles	% missed medication: - Baseline: IG=10%, CG=6% - Post-treatment: IG=8%, CG=4% - No sign. differences between groups

Haberer et al. (2016) [211]	%MA: number monitor opening signals received/ signals expected	Digital	9 months	IG1: Scheduled SMS + real-time MA monitoring IG2: Triggered SMS + real-time MA monitoring	Real-time MA monitoring	Mean % MA over 9-months: - IG1=91%, IG2=79%, CG=79% - ↑ MA in IG1 vs. CG - Similar MA in IG2 & CG
Hardy et al. (2011) [212]	% MA: 1) Self-report 2) Pill count 3) MEMS 4) CAS	Digital	6 weeks	ARemind	BP	Mean % MA-Baseline: - Pill Count: IG=65.2% vs. CG=64% - Self-Report: IG=83.4% vs. CG=74.2% MA-Post-Treatment: - MEMS: - IG=89.7% vs. CG=56.3% - Difference=33.4 (95% CI: 14.1–52.6), p<0.01 - Pill Count: - IG=82.7% vs. CG=69.1% - Difference=13.7 (95% CI: -6.7–34.1), p>.05 - Self-Report: - IG=92.6% vs. CG=72.4% - Difference=20.2 (95% CI: -1.8–42.1), p>.05 - CAS: - IG=83.4% vs. CG=56.3% - Difference=27.1 (7.6–46.6), p<0.05
Hersch et al. (2013) [213]	NR	Digital	9 months	Life-Steps for Managing Medication and Stress: 9 informational, problem-solving and CBT steps	Wait-list	- MEMS: - IG sign. positive effect on MA (CG: unstandardized effect=-0.06, p<0.001; IG: unstandardized effect=-0.03, p<0.01) - No sign. differences for self-report measure
Holstad et al. (2011) [214]	% doses taken, % doses taken on schedule	Face-to-face	8 weeks	KHARMA: using MI	HPP: health education techniques, nutrition, exercise, stress recognition & health issues	Mean % of Doses Taken - Baseline: IG=73.5% vs. CG=74.9% Mean % of Doses Taken on Schedule - Baseline: IG=58.2% vs. CG=59.5% - 3 months: IG=59.4% vs. CG=43.1% - 6 months: IG=55.0% vs. CG=40.1%

						- IG: ↑ % of Doses Taken & % of Doses Taken on Schedule - Sign. decline in MA in both groups over time: % Doses Taken ($F(4,660)=19.04$, $p<.0005$) & % Doses Taken on Schedule ($F(4,667)=23.45$, $p<.0005$)
Johnson et al. (2007) [215]	Low MA: taken doses <85%	Face-to-face	15 months	Healthy Living Project: CBT intervention	No active psychosocial intervention	- % Overall MA=58% - % MA in IG=56.9% - % MA in CG=59% - Sign. difference in MA between IG vs. CG at months 5 and 15
Kalichman et al. (2016) [216]	MA: taken doses ≥90%	Digital	12 months	MA support counseling: MI techniques, reinforcement	Contact-matched counseling: general health & well-being	Baseline MNA: - Overall=82% - IG=80.3% - CG=83.1% Post-treatment MNA: - Overall=65.7% - IG=63.6% - CG=67.1% - Sign. effect of IG over time (Wald $X^2=26.83$, $p<0.01$) - ↑ improvements in IG
Konkle-Parker et al. (2014) [217]	MA: 1) VAS ≥90 2) Pharmacy refills≥90%	Digital	6 months	1) MI: mostly telephone calls addressing motivation, reminders 2) UC	UC	VAS-MNA: - Baseline: IG=40% vs. CG=29% - Post-treatment: IG=51% vs. CG=35% - No sign. differences between groups
Levin et al. (2006) [218]	Cumulative MA: Average % MA of all previous visits	Both	24 weeks	1) Printed card for ART with color picture, dosing schedule & side effects 2) Pillbox 3) Bimonthly postal mailings with motivational messages & reminders	Routine Care	Median Cumulative MA: - IG=96.7% - CG=97.4% - Greater variation in CG ($p<0.05$)
Mao et al. (2018) [219]	NR	Digital	6 weeks	1) IG1: 2-way SMS reminders 3 times per week	Non-specific greeting messages	- 100% MA: 82.3% in previous week

				2) IG2: 2-way SMS reminders 2 times per week		- Post-treatment → no sign. differences between groups (IG1=81%, IG2=94.7%, CG=72.7%)
Murphy et al. (2002) [220]	% dose MA, schedule MA	Face-to-face	7 weeks	1) CBT 2) SC	SC	Mean % dose MA: - Baseline: IG=69% vs. CG=62% - Post-treatment: IG=87% vs. CG=87% Mean schedule MA: - Baseline: IG=3.71 vs. CG=3.93 - Post-treatment: IG=1.82 vs. CG=1.63 - No sign. difference between groups over time
Murphy et al. (2007) [221]	NR	Face-to-face	5 weeks	CBT	SC	- Mean MA-3-month Follow-up: - MEMS: IG (55.2) vs. CG (67.7) - Pill Count: IG (79.3) vs. CG (87.9) - CG had ↑ MA
Nsagha et al. (2016) [222]	% missed treatment for 1 month	Digital	4 weeks	1) Educative SMS messages 2) Standard treatment & care	SC	- IG: MNA=35.6% - CG: MN=55.8% - ↑overall MA at post-treatment: - MNA (baseline)=42.2% - MNA (post-treatment)=45.5%
Pagan-Ortiz et al. (2019) [223]	Perfect MA: no to all questions	Digital	8 weeks	Text-based mobile phone: reminders, health education, motivational messages	N/A	- Differences were sign.: - Baseline MNA: 62% - Post-treatment MNA: 14%
Pop-Eleches et al. (2011) [224]	MA: ≥90% during 12-weeks	Digital	48 weeks	Text messages: barriers to MA, reminders	No messages	MA in CG: - Weeks 1-12: 60% - Weeks 13-24: 51% - Weeks 25-36: 48% - Weeks 37-48: 46% - Weeks 1-48: 40% MA in IG (ITT analysis): - Weeks 1-12: 6% - Weeks 13-24: 58% - Weeks 25-36: 54% - Weeks 37-48: 54% - Weeks 1-48: 53% - Sign. ↑ MA in IG vs. CG

Rodrigues et al. (2012) [225]	Adequate MA: taken doses ≥95%	Digital	6 months	MA support + reminders	N/A	% MA: - Baseline=85% - 1-month=94% - 3-months=93% - 6-months=91% - 9-months=95% - 12-months=94% - Sign. increase over time
Ruan et al. (2017) [226]	1) CPCRA=% doses taken in past 7 days 2) VAS= Optimal MA≥90%	Digital	6 months	1) SMS: greetings, reminders, MA skills, HIV/AIDS & medication knowledge, jokes, motivation 2) UC	UC	VAS-MA: - IG: Pre-treatment=91.3%, Post-treatment=98.7% - CG: Pre-treatment=91.8%, Post-treatment=93.1% - Sign. ↑ in IG vs. CG (Z=2.74, p<0.01) Suboptimal MNA (CPCRA): - IG: Pre-treatment=16%, Post-treatment=10.7% - CG: Pre-treatment=40%, Post-treatment=27.7% - ↓ in IG vs. CG. (Z=2.21, p<0.05)
Safren et al. (2001) [227]	% pills taken in past 2 weeks	Face-to-Face	12 weeks	Life-steps: CBT, problem-solving & MI techniques	Self-monitoring: daily diaries with medication taken	- Mean MA: - IG: Baseline=74%, 2-weeks=95%, Post-treatment=94% - CG: Baseline=84%, 2-weeks=90%, Post-treatment=93% - Sign. main effect for time from Week 0 to Week 12 [F(1,51)=10.64, p<0.01], but no sign. main effect for condition & interaction of time and condition across groups
Scharer et al. (2019) [228]	NR	Face-to-face	4 weeks	1) PATCH: MI techniques 2) SC	SRSP: relaxation skills, coping strategies with depression, problem solving, anger techniques	Missed dose 1+ times per week: - Baseline: IG (64.7%) vs. CG (52.9%) - Post-treatment: IG (13.3%) vs. CG (28.6%) - No sign. differences between conditions

Swendeman et al. (2015) [229]	% doses missed over past 3 days & prior weekend	Digital	1 month	Messages: reminders & CBT messages	N/A	- % doses missed: Baseline=39% Post-treatment=18% - Sign. increase in MA past 3 days ($p<0.05$) & time since missed last dose ($p<0.05$)
Watakakosol (2011) [230]	% dose MA % schedule MA	Digital	5 weeks	Telephone-administered MI+diary	Self-monitoring: daily diaries with medication taken	Mean % dose MA: - Baseline: IG (95.9%) vs. CG (98.5%) - Post-treatment: IG (94.2%) vs. CG (97.6%) Mean % schedule MA: - Baseline: IG (73.1%) vs. CG (77.4%) - Post-treatment: IG (79.9%) vs. CG (82.9%) - % of schedule MA increased over time for both groups, $F(1,38)=7.68$, $p<0.05$ - No sign. findings between conditions
Znoj et al. (2010) [231]	NR	Face-to-face	12 months	1) CBT 2) SC	SC	- Post-Treatment MA: - IG= 69.6% - CG=20.8% - Sign. effect of IG to MA
Hypertension[3] (n=12)						
da Costa et al. (2005) [232]	Pill count: -MNA: pills taken< 80%	Digital	3 months	Reminder card	No reminder card	IG: pre to post -97.1% → 97.3% CG: pre to post -94.9% → 87.3% -↑MA for IG vs. CG: pre-post (difference 95% CI: 1.3 to 18.6)
Davidson et al., (2015) [233]	MA: average daily scores (0-1)	Digital	6 months	SMASH: reminders, personalized motivational & feedback messages, reinforcement messages	SC	-↑MA in IG pre-post (M=0.92 (SD=0.09)) compared to CG (M=0.98 (SD=0.03))
Hacihasanoğlu & Gözüm (2011) [234]	NR	Face-to-face	6 months	1) Group A (Education in MA): education, information about healthy lifestyle behaviours, nursing education (unstructured non-pharmacological treatment & structured MA treatment)	Blood pressure & weight measurements	- Group B & Group A more effective than CG - Group B more effective than Group A

				2) Group B (Education in MA & healthy lifestyle behaviours): education on MA & healthy lifestyle behaviours, nursing education (structured non-pharmacological treatment & MA treatment)		
Hamet et al. (2003) [235]	MA: comparison between rate & time to discontinuation	Digital	12 months	Avapromise intervention: reinforcement (reminder letters, blood pressure diaries, telephone nurse counselling sessions), lifestyle management (educational brochures)	UC educational materials	- MA at post-treatment: 77% IG vs. 76% CG - No sign. differences between IG & CG
Márquez Contreras et al. (2019) [236]	Adherent: AP=80-100% 1) Global MA: AP=80-100% 2) Daily MA: AP=80-100% 3) Correct time MA: AP=80-100% 4) Therapeutic cover MA: AP=80-100%	Digital	12 months	AlerHTA: health education in AHT, reminders	UC: control of blood pressure, therapeutic MA, annual analysis & biannual electrocardiogram	Global MA - 77.02% (95% CI: 70.25–83.79) Daily MA - Total sample: 74.32% (95% CI: 67.29–81.35) - IG: 6 months= 93.15% & 12 months=86.3% - CG: 6 months=70.66% & 12 months=62.66% - % MA: sign. ↑ in IG
Maslakpak & Safaie (2016) [237]	NR	Digital	3 months	Text messaging group: MA educational messages, treatment regimen, physical activities, blood pressure monitoring	1) Reminder cards: MA education, treatment regimen, physical activities, blood pressure monitoring & ordering of cards 2) SE	- Sign. differences between groups at post mean score: text messaging (M=57.70 (SD=2.75)), reminder cards (M=57.51 (SD=2.69)) vs. SE (M=46.63 (SD=2.99))
Mirniam et al. (2019) [238]	MMAS-8 - Low=<6 - Medium=6-7 - High=8	Digital	4 weeks	1) Training sessions: MI, education on medications 2) Phone calls: reinforcement, family support strengthening 3) Medication reminder box	Waiting list	IG: baseline to post - M=3.86 (SD=1.75) → M=6.77 (SD=1.39) CG: baseline to post - M=3.75 (SD=1.46) → M=3.38 (SD=0.99) - ↑ improvement in IG vs. CG

						- IG: Mean Change=2.91 (SD=1.64) - CG: Mean Change=-0.36 (SD=1.15)
Patel et al. (2013) [239]	1) MMAS-4: ↑ scores ↑MA 2) PDC: days access to medication in time period 3) "Weighted" MA: average taken pills	Digital	3 months	Pill phone application: medication reminder	N/A	MMAS-4: - Post sign. increase in MA (t=-5.2) PDC: - Pre-post sign. differences (F=6.4) Pill-phone app: - "Taken" medication: week 1: M=63% vs. week 12: M=54%
Petry et al. (2015) [240]	NR	Digital	3 months	SC+reinforcement: money each time recording medication ingestion within dosing window	SC: see physician as usual	Pill count MA: - ↑ in IG during (F(1,25)=11.57; d=0.94) & after therapy (F(1,20)=15.36, d=1.08) MMAS: - ↑ increase in IG during (F(1,27)=23.57) & after therapy (F(1,26)=19.90)
Ruppar (2009) [241]	MEMS: extent medications corresponds with recommendations of provider	Face-to-face	8 weeks	5 components: medication feedback, hypertension feedback, medication-taking skills, habit adjustment, succinct medication & disease information	UC	IG - Pre (M=66.80 (SD=26.22)) vs. Post (M=81.14 (SD=33.26)) - Significant improvement at post-treatment (Mchange=12.80 (SD=13.78)) CG - Pre (M=37.06 (SD=29.02)) vs. Post (M=36.00 (SD=37.71)) - Significant worsening at post-treatment (Mchange=-1.06 (SD=15.59))
Sheilini et al. (2020) [242]	MMAS-8 - Low=<6 - Medium=6-7 - High=8	Both	3 months	Multimodal: MA information, teaching & healthy lifestyle, reminders	Routine care	IG: baseline to post - M=5.59 → M=7.93 CG: baseline to post - M=5.93 → M=7.60 - ↑ improvement in IG vs. CG (F(1.75, 214.30)=774.18, p<0.001)

Varleta et al. (2017) [243]	MA: Respond positively to 4 MGL questions	Digital	6 months	SMS messages: education, importance of MA	No SMS messages	- IG improved MA by 30% at post-treatment - IG: Pre (49%) → Post (62.3%) - No sign. change for CG (pre: 59.3% vs. post: 51.4%)

Note. AACTG= Adult AIDS Clinical Trials Group; AOR=Adjusted odds ratio; AVR= Automated voice recording; AP= MA percentage; ARemind= Cellular Phone-based Reminder System; ARMS= MA to Refills & Medication Scale; ASK-20= MA Starts with Knowledge; BP= One-way Pager/Beeper; CAS= Composite MA Score; CPCRA= Community Programs for Clinical Research on AIDS; ES=Effect Size; M=Mean; MA= Medication MA; MEMS= Medication Event Monitoring System; MF/F= Mometasone furoate/formoterol; MGL= Morisky-Green-Levine questionnaire; MMAS= Morisky Medication MA scale; PDC= Proportion of days covered; PMAQ= Patient Medication MA Questionnaire; SD=Standard Deviation; SDSCA-MS=Self-Care Activities medications subscale; VAS= Visual Analog Scale.

[1]Digital included reminders, text messages, applications; face-to-face included interventions which were administered in person; whereas both included both digital and face-to-face interventions.

[2]CG=Control Group; CBT= Cognitive-Behavioral Therapy; CIAS= Computerized Intervention Authoring Software; CON=Control phase; eLS= Electronic Life Steps; EMA= Ecological Momentary Assessment; HL= Health literacy; HPP= Health Promotion Program; IG=Intervention Group; IVR= Interactive Voice Response; KHARMA= Keeping Healthy and Active with Risk Reduction and Medication MA; mAMS= Medication MA Management System; MED= MEssaging for Diabetes; MI= Motivational Interviewing; MI-based PEP= Motivational Interviewing-based patient empowerment program; MON=Monitoring Phase; N/A= Not applicable; PATCH= Personal Approach to Treatment Choices for HIV; RTMM= Real Time Medication Monitoring; SC= Standard Care; SE= Standard education; SMASH= Smartphone Medication MA Stops Hypertension; SRSP= Stress Reduction Skills Program; UC= Usual Care.

[3]Studies are listed alphabetically based on condition and then by the names of the authors.

Appendix I

Table 5

Recommendations for Researchers, Clinicians, Healthcare Providers and Staff to improve Medication Adherence

Assessment of MA		- Present clear functional definition of MA and MNA. - Use validated cut-off scores based on the recommendations of creators of each self-reported questionnaire & empirical findings. - Add more objective measures to triangulate MA data (e.g., electronic measurements, pill counts, pharmacy claims). - Screen for barriers to MA and especially for comorbidities (both psychological and medical). - Examine whether MNA is intentional (e.g., negative beliefs on the usefulness of the drug) or unintentional (e.g., forgetfulness).
Intervention targets based on identified barriers and facilitators of MA	*Socioeconomic*	- Consider user-engagement parameters - Personalize & tailor interventions - Build trusting relationships especially with younger patients with low education and income. - Contribute to relieving medication costs where possible; Utilize available programs (e.g. generic medications or patient-assistance programs). - Use digital means of delivering effective interventions, especially for patients with difficulties accessing hospitals or clinics. - Incorporate technological aspects such as videos and promote the participation in online forums interacting with people with similar experiences in order to engage younger patients.
	Therapy-related	- Educate and provide support to the family and significant others on the health condition, its chronicity, necessity and importance of taking medications as prescribed. - Include family members and children (when possible and if desired by the patient) in the intervention as they can often assist with medication taking. - Initiate prevention interventions on alcohol use in patients with HIV/AIDS. - Provide tailored and easy-to-understand information regarding side effects of the prescribed medications, addressing myths regarding side-effects, and exploring the benefits over the costs of taking them. - Provide patients with simplified instructions about the medication regimen, the benefits when taking it and the consequences when not. For patients with asthma, education on how to use medication devices should be specifically provided. - Simplify instructions of medication regiment and provide means (e.g., reminders) for correct following of the regiment. - Prepare for long-term treatment and plan for long-term management and MA. - Prefer using combination therapies instead of multiple medication in patients with diabetes and hypertension.

Condition-related	- In case that comorbidities involve psychiatric disorders (e.g., depression, anxiety), refer to specialists (e.g., psychologists). Interventions with demonstrated effective include Cognitive-Behavioral Therapy (CBT) and Acceptance and Commitment Therapy (ACT). - Provide the patient with simple, useful and relevant information on the diagnosed condition, its implications (e.g., lifestyle changes, symptoms like pain) and advise on how to live with the chronic condition (e.g., support groups, adopting a healthier lifestyle). - Advice on health lifestyle and living with the chronic health condition. - Provide information regarding additional support (e.g., nutritional, physical therapy, patient support groups).
Patient-related	- Address fears and beliefs that constitute intentional barriers to MA, including addressing side-effects and possibility of addiction. - Tailor the intervention based on personalized barriers. - Provide reminders for unintentional MNA (e.g., forgetfulness).
Health-care & system-related	- Adopt a patient-centered approach, where patients in collaboration with health care providers make shared decisions on medication management, discuss concerns and resolve fears.

Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	1, Cover page
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	3-5
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	5
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	6
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	6-7
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	6
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	Appendix B
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	6-7
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	7-8
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	7, Appendix C
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	-

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	7-8
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	8, Figure 1
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	8, Appendix D
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	-
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	Appendices F-H
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	9-11
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	11-13
Limitations	20	Discuss the limitations of the scoping review process.	15
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	14-15
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	Cover page

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850.

Dear Dr. Riley and Dr. Miller,

On behalf of the author team, I would like to thank you for giving us the opportunity to revise and resubmit our work to Translational Behavioral Medicine. We would also like to thank the reviewers for their comments, which we believe have greatly improved our manuscript.

Below you can find a detailed response to all reviewers' comments. Changes relating to reviewer comments in the manuscript were done using yellow highlight color for ease of identification.

Thank you.
On behalf of the author team,

Maria Karekla, PhD

Reviewer #1:

1) Abstract-Purpose "Based on the MAM..." not to

As the reviewer correctly identified, this was a typo and was corrected as suggested.

2) Implications - when discussing interventions may want to add "behavioral health" somewhere so that intervention term is specific to behavior change; think about changing "fear" to concerns.

The intervention term was changed to specify "behavioral health" interventions throughout the manuscript. We have retained both terms 'fear' and 'concerns' as both were mentioned in the included papers as such so to emphasize that both can be patient-related barriers to medication adherence.

3) P. 4 - can you provide one more example of an intervention (e.g. CBT.....)

As suggested, one more intervention example was added. We also made an effort to provide more broad examples of interventions based on social cognitive models like the Theory of Planned Behavior:

'Behavioral health interventions are based on psychotherapeutic approaches (e.g., Cognitive Behavioral Therapy [CBT], Acceptance and Commitment Therapy [ACT]) or other social and cognitive models (e.g. Theory of Planned Behavior)…'

4) p.5- when say "synthesizing evidence for barriers; can add facilitators here too? The emphasis is on the barriers which are many, however, it would be optimal if spoke about facilitators too and this would be throughout the paper

Based on the reviewer's suggestion, the term "facilitators" was added in page 5. This was also changed throughout the paper and we ensured that the paper focus was on both barriers and facilitators to MA.

5) p. 8 - The characteristics addressed make it clear that more studies have been in done in some areas more than others, can you add a discussion point in the Discussion about that discrepancy and the need for more representation of all chronic illnesses reviewed?

Discussion points were added regarding this discrepancy of examination of barriers, facilitators and interventions in some conditions more than others. In particular, relevant information was added in the Discussion sections: “Barriers and Facilitators across Conditions” and “Characteristics of Identified Interventions”.

6) p.10 - there is a brief paragraph on facilitators separate from the barriers, just wondering if might be better integrated throughout? Also, would be good if could add more on family as a facilitator in Discussion points

As suggested, facilitators were integrated throughout the Results section “Barriers and Facilitators to MA” and other parts of the manuscript.

In addition, the impact of family support to higher medication adherence was added and further described in the Discussion sections: “Barriers and Facilitators across Conditions” and “Using Barriers and Facilitators in Behavioral Health Intervention Development”.

7) p.12- could you define term "health literacy"?

As suggested, a definition was added in the first paragraph of page 15:

“…i.e., poor understanding of basic health information and services; [38]”

8) p.13 - when discussing characteristics of identified behavioral interventions can you comment on patient-provider communication and family support?

Based on the reviewer’s suggestion, discussion on the impact of the family support and patient-provider communication as intervention components was added particularly in the Discussion.

9) p.15- consider adding a short paragraph on digital versus in person interventions

A paragraph on digital versus in person interventions was added in the Discussion.

10) p.15- sentence saying "directly address barriers and mechanisms - would add barriers, facilitators, and mechanisms; also consider specifying "interventions" with behavioral health interventions

As suggested, this change was made. Also, the term “interventions” was changed into “behavioral health interventions” throughout the paper.

<u>Reviewer #2:</u>

This scoping review summarizes literature on medication nonadherence in patients who have one of several chronic diseases for which medication nonadherence is most common. The findings are structured around the WHO framework of factors that affect nonadherence. The authors call for multicomponent interventions to address common barriers. The methods are straightforward and the tables detailed. In this reviewer's opinion, however,

the authors have not taken an approach or generated a conclusion that advances current knowledge in this field. Indeed, the findings and conclusions are identical to that of many other systematic reviews. The cited ways in which this review differs from others are not compelling. What is needed is a more critical examination of the problems with existing studies to generate actionable plans for moving the field forward. This is missing from this report.

Thank you for this important comment and for allowing us to edit the manuscript so to make a stronger effort to express how we aim to advance current knowledge in the field. This was exactly our argument when designing this study: that the literature has been critically evaluated but we needed a mapping technique to collate evidence from diverse studies which is exactly the purpose of scoping reviews. We think that by following your recommendations we are now making it clearer what this scoping review offers beyond what is currently known throughout the paper. For example, this is the first paper to examine barriers and facilitators utilizing the WHO dimensions examining them across those chronic conditions that reportedly are found to have the highest medication non-adherence rates. It is also the first to link these with behavioral health intervention findings on how to combat MNA and provides recommendations for both researchers and clinicians who are interested in helping improve MA. Thus this scoping review presented and analyzed gaps in knowledge and identified areas where future researchers and clinicians can take off and also translate for policymaking work.

Major comments

1) There are many directions this review could take to try to push the field forward, a few of which will be mentioned. The authors provide a list of barriers to adherence but have not addressed the fact that some are not modifiable or would be difficult (logistically if not ethically) to intervene on, such as younger age or lower education or income. What attempts have been made to intervene on patients with these characteristics? Citing these barriers also seems to put the blame on patients with these characteristics without asking what healthcare providers and policy can do to facilitate adherence for these patients.

This is a very important point and we are in total agreement with the reviewer. We have now added in the Discussion to highlight this issue as well as explaining why it is important to know that non-modifiable factors impact adherence. Based on the reviewer's suggestion, we have also explained in more detail in Discussion section "Using Barriers and Facilitators in Behavioral Health Intervention Development" what attempts can be made to differently intervene in characteristics and sociodemographic factors that are not modifiable and are associated with higher MNA.

Additionally, recommendations to healthcare providers and policymakers were added to facilitate adherence even in cases when barriers are non-modifiable. Please see particularly the Discussion section "Using Barriers and Facilitators in Behavioral Health Intervention Development" and in Appendix I.

2) The authors note in the Discussion that medication adherence costs should be reduced, but that will not happen any time soon, at least not in the US. What, then, can be done to improve

adherence among patients who cannot afford medications? There is literature on this issue in many areas such as pharmacy and medicine.

This is indeed important and we agree on the point about costs of medication. More recommendations and relevant literature were added in the Discussion section "Using Barriers and Facilitators in Behavioral Health Intervention Development".

"We recognize that medication costs can not necessarily be reduced in many parts of the world, thus when possible, healthcare providers may distribute free samples, help patients access medication discounts, and prefer combination therapies vs. multiple medications [49]."

3) The authors do not distinguish between multi component and single component interventions. Historically many interventions have taken a one-size-fits-all approach, addressing only a single barrier to adherence. Many authors have written about this and suggested that interventions need to be able to address varying (both between and within persons) reasons for nonadherence. Another way of moving this field forward would be discuss nonadherence among patients with multiple chronic conditions. Most patients with diabetes also have hypertension. Is studying adherence in each disease as a silo the way to do this?

We agree with the reviewer and we definitely wanted to make the case as suggested. We added information and description of multi-component and single component interventions in the Results section "Behavioral Health Interventions and Techniques Used for MA":

"Multicomponent interventions (n=36, 64.3%) were mostly administrated followed by single component interventions (n=20, 35.7%). The most common multicomponent interventions were reminders plus educational/reinforcement/motivational messages (n=15, 28.8%), motivational interviewing (MI; n=7, 12.5%) and CBT (n=4, 7.1%). Single component interventions included reminders (n=11, 19.6%), education on condition and medication (n=5, 8.9%) and reinforcement/motivational messages (n=4, 7.1%)."

We also highlighted these points in the discussion section. Furthermore, as the reviewer correctly recommends, a way of moving this field forward is to discuss nonadherence among patients with multiple chronic conditions. This was one of our aims (see section "The Present Study"); however, this was not possible as only one study was included with patients with multiple chronic conditions (i.e., diabetes and hypertension). Therefore, this was further described and added as a suggestion for future researchers in the Discussion section "Characteristics of Identified Interventions":

"It is evident from this review that there is a discrepancy and a need for interventions targeting several chronic conditions, especially asthma and cancer. Furthermore, current research is limited to the study of single conditions at a time, when comorbidity is common (e.g., diabetes coexisting with hypertension). In our review, no studies were included with patients with comorbid conditions, thus more research is needed in regards to MA in individuals with multiple chronic conditions."

4) Finally, the authors have not addressed the issue of medication adherence measurement. At first blush it may seem unrelated, but this reviewer feels otherwise. The widely varying

estimates of adherence (7-95% for hypertension alone!) is due at least in part to poor measurement. With poor measurement, identifying patients who need intervention, and evaluating effects of interventions, cannot be done with a high level of confidence. It is unclear how these cited studies have measured barriers and intervened on them.

Thanks for your comment and we are totally in agreement regarding the issue of MA measurement. Information on how the included studies measured adherence was added in the Results section "Article Characteristics". In addition, in the first paragraph of the Discussion section we address the issue of heterogeneous medication adherence measurement in included studies and we added the comment as suggested by the reviewer. Also, in Appendix I we provide recommendations on the assessment of medication adherence for improving adherence.

Minor comments

5) The literature review seems incomplete. This reviewer is aware of trials that have attempted to improve nonadherence that included adherence as a primary or secondary outcomes, yet they are not included (a few examples of relevant investigators are Kronish, Bosworth, and Ogedegbe).

Thank you for this suggestion. We understand that it is always possible to miss studies and what is included depends on the keywords used and inclusion and exclusion criteria. We decided early on to include only studies where medication adherence was a primary outcome, and this information we ensured to be clearly explained in the Method section "Study Selection". Yet, we did double check our included studies and did not identify others that we missed. Some of the studies commented on by the reviewer were considered but did not fulfill the inclusion criteria such as the examined chronic conditions were not the ones associated with the highest MA rates. Yet, two of the included studies have Dr. Ogedegbe as an author suggesting that this teams' work has been included in our investigation. Data of the screening procedure are available in Open Science Framework (OSF) in https://osf.io/b3xe7/.

6) When the authors draw inferences about adherence rates from the literature, are they using baseline values for randomized trials? This would seem appropriate but is not stated.

Yes, we have used the baseline values from all studies including randomized trials. We have added this information in the Results section "Article Characteristics" and in the first paragraph in the Discussion section.

7) The authors mention that having children is a facilitator of adherence but have not explained why. In the HIV literature, having children can both facilitate and impede adherence. Several systematic reviews and writings by investigators have addressed this issue in depth.

As the reviewer correctly presents, there is HIV-related literature supporting that having children can act both as a barrier and facilitator to MA. We have added this literature, with a number of reasons underling this finding and recommendations in the Discussion section "Barriers and Facilitators across Conditions".

8) Digital intervention is a mode of delivery. The authors combine it with intervention content. It would be important to determine intervention components that might lead to adherence,

and a separate question is how to deliver those components. What are the text messages trying to achieve? Which barriers are they targeting, and which behavior change techniques?

As correctly suggested, we have distinguished the mode of delivery from intervention content throughout the paper. Additionally, we have added and clearly explained which intervention components are effective and their delivery mode in the Results section "Behavioral Health Interventions and Techniques Used for MA".

Reviewer #3:

The authors clearly put a great deal of work into this manuscript, going far beyond typical background reading for a single study. The authors attempt to evaluate multi-level barriers and facilitators to medication adherence across multiple conditions and treatments and in multiple populations (individual, societal, and structural characteristics), in quantitative and qualitative studies, with multiple designs (observational and experimental), and evaluate intervention strategies for improving adherence across all of these factors.

We would like to thank the reviewer for recognizing the great deal of work which we have put in this manuscript.

My main concern is that this manuscript attempts to do too much, so that insufficient attention is given to each research question encapsulated by this review to strongly contribute to the literature. The authors have gained an understanding of the existing research done on predictors of medication adherence, but the information provided in this review doesn't provide "actionable" information, that other researchers could build from—for either narrowing focus for future research (i.e., to identify causal mechanisms of non-adherence) or selecting intervention strategies.

Thank you for the comment and we recognize that a scoping review may often seem to try to do many things. We do recognize this, but we also think that because of the diversity of the literature in this field in terms of research design and measurement methods (among others), a broad scoping review can provide information useful for future research. We have attempted to ensure that findings from this review provide actionable information for research, clinical practice and policymaking.

We think the reviewer's comment on suggesting future researchers to narrow down the focus to the causal mechanisms of non-adherence is important, and we have provided this suggestion in the Discussion.

1) Regarding the former (identifying causal mechanisms of non-adherence): the review does not provide a unifying theory that helps to synthesize the existing evidence to better understand potential causal factors. The reader only knows what generally predicts adherence from a pool of factors that others have studied. For example, younger age (under 30) was associated with poorer adherence, but the reader isn't any closer to knowing why. Is it because younger adults hold different beliefs than older adults, that the medications taken by younger adults are different in their barriers (cost, side effects) than those taken by older adults, or that younger adults with chronic illness have lower levels of education than older adults with

chronic illness (etc)? The method doesn't seem rigorous enough to even conclude that younger age is a consistent barrier to adherence, because there wasn't a targeted analysis of the conditions in which age is more/less influential on adherence. Nor is there an analysis of the relative importance of different factors, since none of the reviewed studies evaluated all of the proposed factors (and this review is not a meta-analysis). Perhaps if the MAM theory is used to drive the synthesis rather than the WHO framework.

Thanks for your comment. Based on the reviewer's suggestion, we have added relevant information in the Discussion section "Barriers and Facilitators across Conditions", explaining where possible why some factors are associated with higher non-adherence rates. However, this was not the objective of this review and we have provided the rationale why a scoping review was preferred because the emphasis was to examine and clarify key definitions in the literature, identify types of available evidence and key characteristics of factors, and analyze gaps in knowledge. Scoping review was also preferred as we sought to inform practice in the field and the way the research has been conducted (Munn et al., 2018). As suggested by the reviewer we have provided a guidance for future research in synthesizing the causal mechanisms of MNA because we think this is very important. We agree that some of the questions posed by the reviewer would better be answered with a meta-analysis, but we think this would be a next step to what we aimed to do with this paper.

Additionally, the WHO framework was preferred to drive the synthesis of the focus of the scoping review into translational evidence to practice rather than updating theoretical evidence (which is the purpose of a systematic review and where a theory like MAM would be more appropriate). The WHO framework clearly explains, organizes and categorizes the factors associated with medication adherence (see Introduction section "Barriers associated with MNA") and we mapped the evidence into this categorization.

2) Regarding the latter (intervention strategies), the reader learns from this review what others have tried but not how each strategy works relative to others, for particular conditions and populations. Whether a provider/researcher works with a specific population and a specific condition or multiple conditions and a diverse population, there isn't enough evidence to narrow down their intervention strategy options.

As suggested, more information was added providing information on which intervention strategies work across and for particular chronic condition, in the Results section "Behavioral Health Interventions and Techniques Used for MA". For example:

"Overall, most of the included studies delivered interventions digitally (n=38, 67.9%), followed by face-to-face (n=13, 23.2%) and both delivery modes (n=5, 8.9%). Multicomponent interventions (n=36, 64.3%) were mostly administrated followed by single component interventions (n=20, 35.7%). The most common multicomponent interventions were reminders plus educational/reinforcement/motivational messages (n=15, 28.8%), motivational interviewing (MI; n=7, 12.5%) and CBT (n=4, 7.1%). Single component interventions included reminders (n=11, 19.6%), education on condition and medication (n=5, 8.9%) and reinforcement/motivational messages (n=4, 7.1%)."

Also, in the Discussion section “Characteristics of Identified Interventions”:

“Clinicians and especially those working with patients with HIV/AIDS and diabetes, should prefer using a combination of reminders with messages including motivation, psychoeducation and CBT techniques than reminders alone. Other effective interventions for patients with HIV/AIDS included CBT and problem-solving techniques.”

“Interventions involving family members and improving the communication between the patient and the healthcare provider and system are of particular importance as most interventions target patients without involving their social and medical support systems [1, 25, 36].”

3) As the authors present, medication adherence and non-adherence are complex topics and multi-determined. The causes of non-adherence and the strategies for improving adherence likely depend on the condition, the population (including individual characteristics and social and structural characteristics), and the treatment. A more targeted analysis of adherence factors and intervention strategies is warranted.

Barriers to medication adherence and intervention strategies across and for particular conditions were added in the Results sections “Barriers and Facilitators to MA”:

[example]: *“When conditions were also examined separately, a commonly reported barrier in studies including patients with HIV/AIDS consisted of greater alcohol consumption. Regarding facilitators to MA, common socioeconomic-related factors across conditions included higher education level, higher socioeconomic status, having children, good social support, and presence of family members who take care and remind them to take medications.”*

and “Behavioral Health Interventions and Techniques Used for MA”:

“Overall, most of the included studies delivered interventions digitally (n=38, 67.9%), followed by face-to-face (n=13, 23.2%) and both delivery modes (n=5, 8.9%). Multicomponent interventions (n=36, 64.3%) were mostly administrated followed by single component interventions (n=20, 35.7%). The most common multicomponent interventions were reminders plus educational/reinforcement/motivational messages (n=15, 28.8%), motivational interviewing (MI; n=7, 12.5%) and CBT (n=4, 7.1%). Single component interventions included reminders (n=11, 19.6%), education on condition and medication (n=5, 8.9%) and reinforcement/motivational messages (n=4, 7.1%).”

Also, a discussion of these findings was added in Discussion sections “Barriers and Facilitators across Conditions” and “Characteristics of Identified Interventions”.

4) It is possible that much greater detail in support of each research question/conclusion could strengthen the contribution of this manuscript. As it is, the reader is left to wade through complex Appendices in order to see the original data and/or to blindly accept the authors' interpretation of the qualitative and quantitative literature. Some more specific examples: in the Discussion, the authors claim that the wide variation (4 to 98%) in non-adherence "can be attributed to the type of design…, to the heterogeneity in measurement methods, and in how individuals who are non-adherent are identified"—why are these factors highlighted and not others, such as type of condition, age of participants, and type of treatment, among other non-

adherence factors? What evidence leads the authors to conclude this? Another example, the authors state that "higher prevalence of MNA in patients with lower education levels…[is] probably associated with a poorer understanding of the healthcare providers' instructions…"— this is a speculation on the part of the authors and not robustly evidenced by the data. The issue isn't that the authors are wrong, since it is entirely plausible that low education predicts low adherence through poor understanding of the treatment, etc, but this review doesn't provide evidence to support this claim. I applaud the authors' incredible effort at attempting to accomplish very important tasks for the field. I think to make a useful contribution to the literature, this review and its many objectives require greater rigor and narrower focus in analysis.

We understand and we agree that readers should not have to wade through Appendices to see the original data. We have made an effort to strengthen the Results section (please also see responses to other reviewers' comments) as well as the Discussion section. However, we also needed to account for the page limitations of the journal so that was the reason we provide the more detailed data from the studies in the Appendices. We do hope that now more information is provided with examples from the studies to strengthen our conclusions.

Based on the reviewer's recommendations, a narrower focus in analysis was made supporting each research question/conclusion in order to strengthen the contribution of this manuscript with information added throughout Results and Discussion sections. For example:

"When conditions were also examined separately, a commonly reported barrier in studies including patients with HIV/AIDS consisted of greater alcohol consumption."

"When conditions were also examined separately, in studies including patients with asthma, poor knowledge on how to use the inhaler was commonly reported, whereas in patients with diabetes and hypertension poly-pharmacy was reportedly associated with MNA."

"It is worth mentioning that these components were mostly delivered digitally through SMS/text messages (e.g., reminders, condition and medication education, motivation), targeting the barriers of forgetfulness and health illiteracy on condition and medication. Furthermore, MI resulted in significant improvements of MA when delivered in any mode."

"Certain barriers relating to socioeconomic characteristics, such as younger ages, low education and income, may not be modifiable, however interventions can differentially target these groups and the particular mechanisms that contribute to MNA. Multicomponent behavioral interventions including techniques of CBT, MI, and problem-solving combined with reminders may be effective in young adults [16, 44]. To maximize the benefits of an intervention, the social support system of the patient including providers and family members should be assessed and involved if so desired by the patient [25, 36]. Healthcare providers are advised to use clear and simple language avoiding medical jargon, especially in patients with lower education levels [45]. Additionally, in order to engage younger adults in treatment, providers can incorporate technological aspects such as videos, and promote the participation in online forums interacting with individuals with similar experiences [46]."

In addition, we have added more evidence supporting our arguments for the two examples reported by the reviewer, in the first paragraph of Discussion and in the first paragraph of page 14. Specifically, for the factors underlying the variability of medication adherence rates as well as why lower education levels are associated with lower medication adherence.