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A Systematic Review Comparing Antiretroviral Adherence Descriptive and Intervention Studies

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Abstract

We examined the extent to which studies aimed at testing interventions to improve antiretroviral adherence have targeted the facilitators of and barriers known to affect adherence. Of the 88 reports reviewed, 41 were reports of descriptive studies conducted with U.S. HIV-positive women and 47 were reports of intervention studies conducted with U.S. HIV-positive persons. We extracted from the descriptive studies all findings addressing any factor linked to antiretroviral adherence and from the intervention studies, information on the nature of the intervention, the adherence problem targeted, the persons targeted for the intervention, and the intervention outcomes desired. We discerned congruence between the prominence of substance abuse as a factor identified in the descriptive studies as a barrier to adherence and its prominence as the problem most addressed in those reports of intervention studies that specified the problems targeted for intervention. We also discerned congruence between the prominence of family and provider support as factors identified in the descriptive studies as facilitators of adherence and the presence of social support as an intervention component and outcome variable. Less discernible in the reports of intervention studies was specific attention to other factors prominent in the descriptive studies, which may be due to the complex nature of the problem, individualistic and rationalist slant of interventions, or simply the ways interventions were presented. Our review raises issues about niche standardization and intervention tailoring, targeting, and fidelity.

Reviews of descriptive studies have shown the many and varied factors influencing antiretroviral adherence (e.g., Ammassari et al., 2002; Mills et al., 2006; Vervoort, Borleffs, Hoepelman, & Grypdonck, 2007). Reviews of intervention studies indicate that the active component has yet to be identified that will produce consistently desirable adherence rates (e.g., Rueda et al., 2006; Rivet Amico, Harman, & Johnson, 2006; Simoni, Pearson, Pantalone, Marks, & Crepaz, 2006). The use of diverse measurements of adherence (Liu et al., 2001; Mannheimer et al., 2008; Paterson, Potoski, & Capitano, 2002), and recent findings that the levels of adherence required to achieve viral suppression and prevent drug resistance may vary with drug regimen (e.g., Bangsberg et al., 2006), complicate efforts to understand and improve adherence.

Intervention studies ought to be firmly grounded in empirically-based understandings of the problems to be targeted (Sidani & Braden, 1998). However, the congruence between factors identified through empirical studies to influence adherence and the targets of interventions designed to enhance adherence has not yet been explored. The purpose of the systematic review reported here was to ascertain the extent to which a set of antiretroviral adherence intervention studies targeted the facilitators of and barriers to adherence identified in a set of antiretroviral adherence descriptive studies.

Method

This systematic review was conducted in the course of a research project aimed at developing methods to synthesize qualitative and quantitative research findings. Search and retrieval procedures were thus selected to accommodate methodological objectives, not to answer research questions about antiretroviral adherence per se. The goal was to obtain a well-defined but manageable sample of research reports with sufficient methodological diversity (i.e., different types of qualitative and quantitative studies) and topical uniformity (all on antiretroviral adherence) to permit the intensive analysis and experimentation with technique required in a study of methods. Specifically, we confined our search to published reports as unpublished reports contained no methodological variation not found in published reports. We confined our search to studies conducted in the United States as national differences in healthcare delivery and attitudes toward HIV infection would have added a level of complexity to analysis that would not advance the methodological aims of our study. We confined our search for descriptive studies to those conducted with women only. Reviews of studies conducted with men and women or men only (e.g., those cited above) indicate no factor influencing adherence not also found in women-only studies. Yet, additional factors are found in women-only studies (e.g., those related to reproduction and mothering); indeed, women's unique circumstances are often cited in reports of women-only studies as justifications for studying women only. Men-only descriptive studies can, thus, be considered a subset of women-only descriptive studies. Antiretroviral intervention studies conducted with women and men can be assumed to address factors common to both. All of these sampling delimitations constitute limitations to the review presented here, yet all systematic reviews entail such limitations (Sandelowski, Voils, & Barroso, 2007).

Forty-one reports of antiretroviral adherence descriptive (14 qualitative and 27 quantitative observational) studies were retrieved between June, 2005 and October, 2007. Forty-seven reports of antiretroviral intervention studies were retrieved in October, 2007. We used electronic databases housing citations to literature across the health, behavioral, and social sciences, including Academic Search Elite, Alternative Press Index, Cochrane Central Register of Controlled Trials, Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsycINFO, PubMed, and Sociological Abstracts. We used variations (e.g., extensions, truncations, synonyms) of the following search terms to accommodate the distinctive features of each of these databases: HIV, AIDS, antiretroviral, adherence, compliance, clinical trial, intervention, and experiment. We augmented electronic searching with the use of ancestry and descendancy approaches (Cooper, 1998), in addition to hand-searching the print collections of our university libraries for books, anthologies, and other documents on HIV/AIDS likely to include relevant reports.

Antiretroviral Descriptive Studies

Reports of descriptive studies were eligible for inclusion if they were of empirical qualitative and quantitative observational studies of adherence to antiretroviral therapy conducted with HIV-positive women of any race/ethnicity, class, or nationality living in the United States, and published in or after 1997 (when protease inhibitors became part of the standard of care) to the

present (2007). We accepted reports of studies conducted with HIV-positive women that included HIV-positive men if an explicit research purpose was to compare women and men in relation to antiretroviral adherence and if the report contained findings focused on women.

We extracted from the qualitative studies all findings addressing any aspect of antiretroviral adherence and calculated their frequency effect sizes, or the number of reports containing a finding divided by the total number of reports (Sandelowski & Barroso, 2007). We extracted from the quantitative observational studies all relationships addressing adherence and another variable, and computed their effect sizes. The effect size index that we used is Cohen's *d* (Cohen, 1988), which is the standardized difference between two means (in these studies, the difference in mean adherence between two groups, such as drug users versus non-users). Calculating *d* enables comparisons to be made across studies because all differences in means are on the same scale. A value of 0 indicates no difference between means. Cohen suggested that values of .20, .50, and .80 represent small, medium, and large differences, respectively. Because we would not expect interventions to address factors that have not been shown to be related to adherence, we excluded findings that did not meet the criterion for a "small" effect size (i.e., any $d < .20$) in quantitative research. We used effect sizes instead of *p*-values, which are influenced by sample size to a greater degree (Rosenthal, 1984). We also excluded findings for which there was insufficient information for calculating an effect size even after contacting the authors. Whenever only bivariate or only multivariable findings were addressed in a report, we retained those findings, but in reports in which the same variable was addressed in both bivariate and multivariable analyses, we used the bivariate relationship. This is because an effect size for a partial relationship may be greater or lesser, depending on which variables are chosen to be included in the multivariable model. Multivariable findings, therefore, are less comparable than bivariate findings because they estimate different partial relationships (Voils, Barroso, Hasselblad, & Sandelowski, 2007).

We then grouped these findings into categories and the findings within these categories into factors favoring adherence and nonadherence. (Tables showing the results of these data extractions and computations are available from the first author on request.)

Antiretroviral Intervention Studies

Reports of intervention studies were eligible for inclusion if they were of studies published in or after 2000 to the present (2007) of any kind of intervention designed to improve antiretroviral adherence in any HIV-positive person living in the United States. We selected the year 2000 to accommodate the time it likely took for findings from adherence descriptive studies to make their way into adherence intervention studies. We included intervention studies conducted with both women and men as too few adherence intervention studies have targeted women only. We included all designs, including randomized controlled trials, nonrandomized studies, and within-subject studies with pre-post tests. We excluded reports of pilot studies if a later report testing the same intervention in a larger sample was available so that each intervention would be counted only once.

We extracted and tabulated information from each report on the nature of the intervention, the adherence problem targeted, the persons targeted for the intervention, and the intervention outcomes desired. Table 1 shows the results of this work.

Report Quality and Procedural Validity

All reports were reviewed by the first two authors, and all extractions, tabulations, and computations of findings were checked by at least two members of the research team, or discussed until consensus was reached in meetings of the entire research team. No reports of qualitative studies that met selection criteria were excluded for reasons of quality per se as any

methodological shortcomings they showed did not invalidate their findings (Sandelowski & Barroso, 2007). Entire reports of quantitative observational studies that met selection criteria, or specific findings in these reports, were excluded only if it was not possible (even with attempts to contact authors) to calculate effect sizes. No reports of intervention studies that met selection criteria were excluded as our goal was not to summarize their findings, but rather the problems and persons targeted for intervention and the interventions tested.

Results

Factors Influencing Adherence in Descriptive Studies

The categories of factors most prominent (i.e., appearing in the largest number of different reports) in favoring adherence were: sociocultural factors (14 reports); relationship with healthcare provider (10 reports); attitudes toward and beliefs about HIV infection and antiretroviral therapy (9 reports); and, medication regimen and motivation/inclination to act (8 reports each). The factors favoring adherence appearing in the largest number of different reports across categories were: having a supportive family and having a supportive provider (6 reports each), and believing in the effectiveness and safety of antiretroviral therapy (5 reports).

The categories of factors most prominent in favoring nonadherence were: medication regimen (14 reports); sociocultural factors, and attitudes toward and beliefs about HIV infection and antiretroviral therapy (12 reports each), and substance abuse (including drug and alcohol abuse, 11 reports). In addition to the 11 reports comprising the substance abuse category, the most prominent factors across categories favoring nonadherence were: having side effects (13 reports); not wanting others to know HIV status (7 reports); and, uncertainty about the effectiveness and safety of antiretroviral medications and having no symptoms from HIV (6 reports each).

Factors Targeted in the Intervention Studies

The primary focus of the intervention reports—to improve adherence to antiretroviral therapy—was operationalized in different ways (e.g., adherence to dose or schedule, as measured by number or percentage of missed pills, self-report, pill counts, or Medication Event Monitoring System caps). Of the 47 reports, 23 featured outcome measures in addition to adherence, such as self-efficacy, social support, and a range of mental health indicators.

As shown in Table 1, the only persons targeted for intervention were HIV-positive persons themselves. Among HIV-positive persons, the primary targets were those with “poor” adherence (11 reports) and having a substance abuse problem (10 reports). In 9 reports, no specific population target was identified other than being HIV-positive. Women were the sole targets in 7 reports (including 1 report featuring women with substance abuse). Of the 40 remaining reports of studies with both men and women participants, in only 5 was sex difference addressed in relation to outcomes; in none of these were sex differences found.

Also as shown in Table 1, 20 of the 47 intervention reports target one specific problem favoring nonadherence, such as forgetting to take medications, depression, substance abuse, risky behaviors, or low health literacy. The problem most targeted in these studies was substance abuse (7 reports, excluding 2 reports that target persons with substance abuse but do not explicitly present substance abuse as an adherence problem). In contrast, the remaining 27 reports target either no specific factor (18 reports) at all or multiple factors influencing adherence (9 reports). The reports with no specific adherence factor identified typically contain reviews of the interventions previously tested to enhance adherence, not of factors found to

favor adherence or nonadherence. The reports featuring multiple factors contain reviews of a host of factors shown or surmised to be related to nonadherence.

As shown in Tables 1 and 2, the interventions tested were either single- or multiple-component. Single-component interventions addressed one domain, such as direct observation of behavior, while multiple-component interventions addressed at least two domains, such as cognitive-behavioral elements directed toward knowledge, beliefs, social support, and behavior. Cognitive-behavioral interventions were the most prevalent interventions, used to address both single problems favoring nonadherence (e.g., substance abuse) and multiple problems favoring nonadherence (e.g., lack of knowledge, forgetting, low self-efficacy).

As shown in Table 2, the most prevalent problem-intervention combination was the *no specific problem/multiple-component* intervention (16 reports), followed by the *single problem/single-component* intervention (12 reports), *multiple problem/multiple-component* intervention (9 reports), *single problem/multiple-component* intervention (8 reports), *no specific problem/single-component* (3 reports, including 1 report testing a single- and a multiple-component intervention), and *multiple problem/single-component* (1 report testing a single- and a multiple-component intervention). Substance abuse is an example of a single problem addressed by single- and multiple-component interventions, including direct observation or administration, contingency management, and cognitive-behavioral therapies. Direct observation or administration is an example of the same intervention tested to address multiple problems, no specific problem (other than poor adherence), and one specific problem (substance abuse).

Discussion

Extent to Which Intervention Studies Targeted Factors Found to Influence Adherence

Substance abuse was prominent as a barrier to adherence in descriptive studies and as a target of intervention in intervention studies. Family and provider support was prominent as a facilitator of adherence in descriptive studies, while social support was an explicit intervention component in 12 of the intervention studies and an outcome variable in one additional study. Social support was an implicit component in all of the interventions as any cognitive-behavioral or psycho-educational intervention constitutes a kind of social support.

Side effects were the most prominent factor found to impede adherence, yet interventions to target them were less discernible in the intervention reports. However, the reduction/elimination of side effects may be more amenable to pharmacological than to cognitive-behavioral or psycho-educational interventions directed toward managing side effects. Despite the prominence of the social environment in facilitating or impeding adherence in the descriptive studies, interventions were directed solely toward HIV-positive persons, not, for example, the healthcare system or societal norms. Intervention components were largely in the cognitive domain, even when directed toward non-cognitive elements as, for example, when an educational, not a social, intervention was directed at teaching HIV-positive persons how to mobilize social support.

Researchers have argued that the overly individualistic and rationalist orientation to antiretroviral adherence cannot adequately address the “hybrid medico-experiential ways of knowing” (Mykhalovskiy, 2008, p. 138) of HIV-positive persons; the daily “health work” (Bresalier et al., 2002) of which antiretroviral adherence is only a part; the varieties of strategic nonadherence that paradoxically permit overall adherence (Broyles, Colbert, & Erlen, 2005); and, the episodic, dose-by-dose nature of medicine taking (Ryan & Wagner, 2003; Wilson, Hutchinson, & Holzemer, 2002). Both descriptive and intervention studies leaned toward the cognitive, but that lean may not capture the ongoing work of medicine taking and the larger sociocultural arena in which this work is embedded.

Targeting, Tailoring, and Fidelity in Antiretroviral Intervention Studies

Our review raises questions regarding the nature of the interventions themselves. Multiple-component interventions were typically presented in reports as especially suitable for addressing the many factors operating against antiretroviral adherence under the apparent assumption that complexity of problem must be matched to complexity of solution: that a shotgun approach to intervention (i.e., involving multiple components, in addition to multiple delivery channels and/or types of providers) will actually hit the one or more problems in play for any one person receiving the intervention at any given time. In 27 of the 47 intervention reports, either no specific problem or an array of problems influencing adherence were addressed. Interventions targeting many problems at once are as non-specific as the ones targeting no problem at all.

When authors described their interventions as tailored, they were most often actually referring to targeting the problems identified by individual participants as impeding their adherence (e.g., forgetting, lack of self-efficacy) with that component of the intervention that was to be mobilized whenever that problem was identified (e.g., memory prompting, skill-building). In some cases, they were referring to an intervention tailored to a particular medication regimen, not a problem or person per se. Targeting and tailoring were further indistinct when researchers described their interventions as intending to meet the special needs of entire social groups, such as women, Latinos, or substance abusers. Researchers were here invoking what Epstein (2007, Ch. 7) referred to as “niche standardization,” whereby both the universalism of assuming that all HIV-positive people are the same, and the individualism of assuming that HIV-positive persons share no common ground with each other, are avoided. Tailoring in the intervention studies reviewed involved interventions delivered to individuals seen to have one primary group membership. At issue is which niches are the least likely to minimize differences essential to enhancing antiretroviral adherence.

The essential incompatibility between intervention tailoring and fidelity (a demonstration that an intervention was delivered as planned) complicates the implementation of tailored interventions. In most cases of tailoring, interventions were customized in a scripted way: for example, if the person expressed a knowledge deficit, the intervention protocol dictated what the interventionist was to do or say to reduce it. Unclear was how far tailoring could go before intervention fidelity was undermined. Intervention fidelity was addressed in 17 of the 27 reports of tailored interventions, but in none of them was the incongruity addressed between the tailoring of interventions and the standardization of interventions required to optimize intervention fidelity.

This raises the questions of how tailored an intervention can be before intervention fidelity is impossible to achieve and researchers can no longer claim they tested any one intervention at all, and whether any multiple-component intervention can be tested as a single experimental condition. Although tailored interventions have been found to be generally superior to control conditions (Richards et al., 2007), yet to be sufficiently differentiated in intervention research is whether it was the content, function, or form of the intervention that was standardized or, conversely, altered to fit (Campbell et al., 2000; Castro, Barrera, & Martinez, 2004; Hawe, Shiell, & Riley, 2004) some individual, social group, or situation. In tailored intervention studies, outcomes would need to be differentiated by the problem identified and the intervention component implemented in response to that problem.

In conclusion, our review suggests some congruence between factors targeted in antiretroviral adherence intervention studies and those identified in descriptive studies as influencing adherence. Lack of congruence may be due to the complex nature of the adherence problem, individualistic and rationalist orientation toward intervention, or simply the way interventions were presented. Our review also raises questions about the relationships among intervention

tailoring, targeting, and fidelity and, in the case of antiretroviral adherence interventions in particular, about how interventions are best structured to capture the ongoing work of adherence and variations in participants, social environment, and type of medication regimen, and to maximize the ability to draw credible conclusions about the effectiveness of interventions for achieving desirable adherence rates.

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Notes. ^d = adherence descriptive study; ⁱ = adherence intervention study

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Table 1

Intervention, and Target Problem, Population, and Outcome in 47 Intervention Studies

Report	Target problem	Target population	Intervention	Outcome measured in addition to adherence
Andrade et al.	Forgetting	Persons with memory dysfunction	Memory prompting device	
Collier et al.	NS	NS	Social support and scripted phone calls	
Dallessandro et al.	Depression	Depressed persons	Antidepressants	
DeFino et al.	NS	Inner-city persons with barriers to adherence	Educational, motivational	
Dieckhaus et al.	NS	Persons with imperfect adherence, at risk for poor adherence	Multi-component (Memory prompting devices, referral, social support, counseling)	
DiIorio et al.	Multiple	Prescribed therapy with at least 1 protease inhibitor	Motivational interviewing	Retention and attendance rates
Garland et al.	NS	Treatment-naïve or with no more than 1 regimen failure	Direct administered therapy	Self-efficacy, coping style, satisfaction with care, trust in provider, social support
Golin et al.	NS	Persons failing or initiating therapy	Motivational interviewing	
Harwell et al.	NS	Women with substance abuse and poor adherence	Direct observation	
Holzemer et al.	Multiple	NS	Multi-component (knowledge, medication-taking patterns, role performance, provider relations)	Psychological wellbeing, self-efficacy
Ironson et al.	Self-efficacy	Minority women	Cognitive-behavioral-stress management	
Javanbakht et al.	Multiple	Persons with poor adherence	Case and contingency management	Coping with stress
Jones et al.	Multiple	Women	Cognitive-behavioral-stress management	Knowledge, intentions to adhere, self-efficacy
Kalichman et al.	Low health literacy	Persons with low health literacy	Informational-motivational-behavioral	
Levin et al.	NS	Persons starting new or changing regimen	Multi-component (medication cards, pillboxes, mailing motivational messages)	
Lucas et al., 2006	Substance abuse	Injection drug users on methadone	Directly administered therapy	Time under direct observation, urine drug screening
Lucas et al., 2007	Substance abuse	Injection drug users on methadone	Directly administered therapy	Knowledge
Lyon et al.	Multiple	Adolescents and young adults	Family & peer group education and support	
Macalino et al.	Substance abuse	Substance abusers	Modified direct observation	Optimism
Mann	Optimism/pessimism	Women	Writing about positive future	
Mannheimer et al.	NS	Therapy-naïve persons initiating therapy	Social support (medication manager) v. electronic reminder system	Sexual & drug-related behavior, addiction severity
Margolin et al.	Risky sexual & drug-related practices	Injection drug users on methadone	Cognitive-behavioral (information, motivation, skill-building)	Methodone concentration
McCance-Katz et al.	Substance abuse	Injection drug users on methadone	Modified direct observation	
Milam et al.	NS	NS	Cognitive-behavioral (preventive messages, education, skill-building, support)	

Report	Target problem	Target population	Intervention	Outcome measured in addition to adherence
Murphy, Lu, et al., 2002	NS	Documented adherence problem	Multi-component (education, behavior change, social support)	Coping, social support, mental health indicators
Murphy, Marelich, et al., 2007	NS	Miss at least 1 dose/week	Social cognitive (knowledge, skill acquisition, self-efficacy, support)	Coping, social support, mental health indicators, substance use, self-efficacy, intention
Parry et al.	Multiple factors	Chronically nonadherent	Cognitive; information, motivation, skill-building	Temptation for drug use
Parsons et al.	Substance abuse	Substance abusers	Cognitive-behavioral, motivational interviewing	Missed phone calls
Puccio et al.	Incorporation of therapy into daily routines	Adolescents and young adults	Cell phone reminders	
Rathbun et al.	NS	NS	Multi-component (education, monitoring, reminder devices)	
Rawlings et al.	Under-represented in research are over-represented among those with HIV	Persons "under-represented" in research	Education and empowerment counseling	
Remien et al.	NS	HIV sero-discordant couples together >6 months & < 80% adherence	Couple-based social support	
Reynolds et al.	NS	NS	Telephone calls (self-care strategies)	
Rigsby et al.	Adherence to dose interval	NS	Cue-dose training and/or cash reinforcement	
Rosen et al.	NS	Persons with histories of substance abuse	Contingency management, substance abuse counseling, on-going review of adherence behavior	Substance abuse
Safren et al.	Forgetting	NS	On-line pager reminder system	
Samet et al.	Alcohol abuse	Persons with histories of alcohol abuse	Multi-component (reminder device, enhancement of self-efficacy, discussion of abuse, counseling)	Alcohol consumption
Simoni et al.	Social support, depression	NS	Peer support	Social support, depression
Smith et al.	Self-efficacy	Persons starting or switching to new regimen	Self-management, social cognitive (information, skill-management, social support)	Self-efficacy
Sorensen et al.	Substance abuse	Persons in methadone maintenance program & <80% adherence	Contingency management	Drug use
van Servellen et al.	Poor access and utilization of services, low health literacy	Low-income Spanish-speaking Latinos	Multi-component, culturally congruent (education, quality of life, risk reduction, communication skills, social support)	Health literacy, relationship with provider
Visnegarwala et al.	Indigence, institutionalization of healthcare	Indigent women newly starting therapy	Directly delivered therapy v. healthcare team strategy	Appointments kept
Wagner et al.	NS	Persons initiating or changing ARV therapy	Cognitive-behavioral/motivational (IMB)	
Westling et al.	Discovery of meaning	Low income women	Future (to enhance optimism and cognitive processing) v. neutral writing	Optimism
Williams et al.	NS	NS	Social support	
Wohl et al.	NS	Persons with 1 prior regimen failure	Direct observation v. case management	
Wyatt et al.	Risk behaviors	Women with histories of child sexual abuse	Cognitive-behavioral	Sexual risk reduction

Notes. NS=no specific problem or target population identified

Table 2

Combinations of Single v. Multiple Problems and Single v. Multiple Component Interventions

Intervention component(s)	Single problem	Problem(s) No specific (NS) or multiple (M) problems
	<u>Single-component</u>	Depression/antidepressants (Dalessandro et al.) Forgetting/memory prompting device (Andrade et al.; Safren et al.) Substance abuse/direct observation or administration (Lucas et al., 2006, 2007; Macalino et al.; McCance-Katz et al.) Substance abuse/contingency management (Sorensen et al.) Low optimism/writing (Mann) Discovery of meaning/writing (Westling et al.) Adherence to dose interval/cue-dose training (Rigsby et al.) Routinization of therapy/memory prompting device (Puccio et al.)
<u>Multiple-component</u>	Low literacy/cognitive-behavioral (Kalichman et al.) Self-efficacy/cognitive-behavioral (Ironson et al.; Smith et al.) Substance abuse/cognitive-behavioral (Parsons et al.; Samet et al.) Risk behaviors/cognitive-behavioral (Margolin et al.; Wyatt et al.) Under-represented in research/education and empowerment counseling (Rawlings et al.)	NS/M (Collier et al.; DeFino et al.; Dieckhaus et al.; Golin et al.; Levin et al.; Mannheimer et al.; Milam et al.; Murphy, Lu, et al., 2002; Murphy, Marelich, et al., 2007; Rathbun et al.; Remien et al.; Reynolds et al.; Rosen et al.; Wagner et al.; Williams et al.; Wohl et al. ^a) M/M (Dilorio et al.; Holzemer et al.; Javanbakht et al.; Jones et al.; Lyon et al.; Parry et al.; Simoni et al.; van Servellen et al.; Visnegarwala et al. ^a)

^aNote. In these studies, two interventions were tested in addition to a standard-of-care condition.