AIDS and Behavior (2019) 23:2219–2225
https://doi.org/10.1007/s10461-019-02650-1

EDITORIAL

When is Enough, Enough? How the Absence of Dose-Determination Trials Impedes Implementation of HIV Behavioral Interventions

Seth C. Kalichman[1]

Published online: 22 August 2019

Abstract
Carefully controlled clinical trials have determined that theory-based behavioral interventions delivered by adherence nurses, professional and paraprofessional counselors, and case managers improve ART adherence and viral suppression. However, there are no studies that empirically inform how much intervention is needed for which patient populations and at what cost. This Editorial raises the issue of how a lack of intervention dosing limits interpretation of trial results and impedes implementation, therefore calling for behavioral intervention dose-finding studies.

Keywords HIV interventions · Adherence interventions · Dosage · Dose-determination · Implementation science

Antiretroviral therapy (ART) effectively manages HIV infection, extends and improves lives, and potentially slows HIV epidemics. Unfortunately, not everyone receiving ART is benefitting from treatment because of poor adherence. Previous estimates suggested that one-in-five people with HIV being treated with ART have unsuppressed virus [1]. However, the CDC now shows that these once concerning estimates were actually overly optimistic. It is more likely that one-in-three people receiving ART (38%) in clinical care do not demonstrate durable viral suppression [2–4]. Globally, ART adherence is essential to achieving UNAIDS goals for controlling HIV epidemics and few countries are on a path to end HIV [5]. Sub-optimal rates of HIV suppression signals an urgent need for patient-centered interventions that directly respond to situations impeding engagement in care and ART adherence [6].

Clinical trials conducted over the past decade, including several studies published in *AIDS and Behavior*, have determined that theory-based behavioral interventions delivered by adherence nurses, professional and paraprofessional counselors, and case managers have the potential to improve ART adherence and viral suppression [7–10]. However, despite statistically significant intervention effects in several efficacy trials, we know that a fixed number of intervention sessions, typically 4-to-6 sessions, is insufficient for many patients to achieve optimal outcomes, namely viral suppression. We also know that some individuals actually achieve optimal outcomes with fewer than an arbitrarily fixed number of intervention sessions. Despite the universally rejected assumption that one-size fits all in behavioral interventions, there are no published trials to empirically determine the appropriate dosing expectations of behavioral interventions for use with key targeted populations.

Behavioral interventions typically assume that the intervention dose can be derived from past trials, which themselves had arbitrarily set the dose. It is therefore likely that many behavioral interventions are not considered efficacious when in fact they may have been under-dosed. Similarly, program managers and funding agencies that lack dosing information require providers to waste resources and deliver a fixed dose of intervention sessions that exceed the amount needed—over-dosing. We would not expect medications taken below therapeutic levels to work and we do not accept the costs incurred by delivering unnecessary amounts of medical services. And yet we ignore the implications of under-dosing and over-dosing behavioral interventions.

✉ Seth C. Kalichman
Seth.k@uconn.edu

[1] Psychological Sciences, University of Connecticut, 2006 Hillside Road, Storrs, CT 06269, USA

Intervention Dose is Not the Same as Intervention Content

How much intervention is needed to achieve optimal outcomes is not the same as the composition of the intervention content. The distinction between intervention content and dose is apparent in behavioral skills interventions. Skills building involves a series of steps and activities including practice/rehearsal of skill enactments, reinforcement, goal setting, etc. The steps or activities involved in skills building speaks to content. Behavioral skills building also requires repeated practice and it is the number of behavioral skills rehearsals enacted that represents dose. In behavioral interventions, content and curriculum constraints have been confused with dose. Curriculum-based interventions are often focused on delivering specific learning objectives and allocating time needed to cover the material needed to reach objectives, a standard approach in education. However, the concept of dose should be differentiated from content. Keeping with a drug development metaphor, the formulation of pharmaceutical agents is analogous to intervention content and is not the same as dose. Content is the 'what' of an intervention, dose is the 'how much' of an intervention. The more flexible an intervention's content, that is the more like client centered counseling and the less like an educational curriculum, the more obvious is the need to determine dose. Scripted curricula are designed to meet learning objectives, whereas unscripted interventions, such as client-centered counseling are directed toward meeting individualized needs. Table 1 shows a sample of client centered ART adherence interventions included in the CDC's Compendium of Evidence-Based Interventions [11]. These interventions share common components in terms of content, and none have empirically-based guidance for dosing.

Retrospective Reviews Cannot Determine Intervention Dose

There have been efforts to determine the dose of behavioral interventions through post hoc or secondary analyses. Unfortunately, retrospective reviews and meta-analyses are unable to determine dosing. For example, in an important meta-analysis of ART adherence interventions, Simoni et al. [12] included a dichotomous variable of intervention dose (5 or more vs. less than 5 sessions) as a covariate of intervention effects. The results did not indicate an effect of 'dose'. However, a dichotomous variable lacks sensitivity for determining dose and the multiple interventions analyzed by Simoni et al. were not designed to determine dose. The interventions also varied in numerous ways including content, context, duration, frequency and amount of intervention. In another effort to determine ART adherence intervention dosing from published clinical trials, Voils et al. [13] examined three parameters of intervention dose; duration—weeks of intervention contact, frequency—number of contacts per week, and amount—minutes of intervention per contact. Voils et al. concluded that there was insufficient information to analyze dose in the ART adherence literature. For example, twelve of the trials examined did not even report the amount of intervention time. Duration of interventions ranged from 1 week to 96 weeks and the modal frequency of contacts was once per week. The implementation and scale-up of evidence-based behavioral interventions has been hampered by: (a) failure to determine the amount of intervention needed to achieve optimal clinical outcomes; (b) a lack of dosing information keyed to population subgroups; and (c) a void of information on the costs associated with intervention dose–response [14].

Fixed-Dose Clinical Trials Mask Critical Dose Information

One of many examples of how arbitrarily set dosing has limited the interpretation of trial findings is offered by a clinical trial that tested behavioral self-regulation counseling to improve ART adherence [15]. In this trial 600 individuals receiving ART who were non-adherent were randomized to receive either: (a) 5-fixed-dose sessions of brief bi-weekly adherence self-regulation counseling (with or without text reminders), or (b) 5-brief contact-matched control sessions (with or without text reminders). The findings showed that the behavioral self-regulation counseling resulted in statistically significant improvements in ART adherence and HIV suppression compared to the contact-matched control condition. However, even with the positive outcomes from counseling, adherence gains were not achieved for more than half of participants receiving counseling. And yet, these suboptimal rates of improvement occurred in the context of statistically significantly better improvement than observed in the control condition.

The majority of adherence counseling interventions are dosed with four or five sessions. However, the rationale for the fixed dose is often unknown. One basis for this dose may be that adherence faces multiple challenges; fewer than five-sessions may just not 'feel' sufficient. On the other hand, every additional session increases the risk that the intervention will not be useful in real world settings; increasing dose comes at a cost.

Table 1 Selected client centered efficacious HIV treatment engagement & adherence intervention

Intervention	Fixed dose	Theoretical basis	Major components
Phone-delivered support for counseling for HIV treatment adherence [15]	Five weekly 20–30 min. sessions	Self-regulation theory	Counseling, corrective feedback, discussion, personalized plan, problem solving, reinforcement, referral
Care + [23]	Four 25-to-30-min sessions delivered at 3-month intervals	Social cognitive theory, transtheoretical model, IMB	Counseling, goal setting, discussion, planning, skills building, problem solving, referral
Sharing medical adherence responsibilities together (SMART) couples [24]	Five weekly 45–60 min. sessions	Self-regulation & social action	Discussion, problem solving
In the mix (ReMix) [25]	Five weekly 30 min. phone sessions	Conflict theory	Goal setting, practice, discussion, planning, problem solving
Point of care CD4 count testing and care facilitation with ARTAS [26]	Up to five phone or in person sessions	None	Strengths-based phone counseling
Healthy living project -adherence module [27]	Five 90-min. sessions delivered over 2-months	Social action theory	Goal setting, practice, discussion, problem solving
Helping enhance adherence to antiretroviral therapy (Project HEART) [28]	Two 2 – 3-hour sessions prior to ART & three 1.5-hour sessions after starting ART	Self-determination theory	Problem solving, discussion, practice, individualized plan
Managed problem solving (MAPS) [29]	On-going	Social cognitive theory	Goal setting, discussion, planning, problem solving
Adherence improving self-management strategy (AIMS) [30]	On-going	Self-regulation, Self-determination, & theory of planned behavior	Corrective feedback, discussion, personalized plan, problem solving
Partnership for health [31]	On-going	Mutual participation	Brief counseling, discussion, problem-solving

Source: CDC compendium of effective treatment engagement & adherence interventions, Accessed August 11, 2019 https://www.cdc.gov/hiv/research/interventionresearch/compendium/index.html

Lack of Dosing Information Impedes Implementation

Implementers and program managers are in need of guidance for behavioral intervention dosing. In the absence of an empirical basis for intervention dosing, funding agencies and program managers are left with few options and require that service providers deliver the number of sessions that the original researchers tested, albeit without an empirical basis. Once implemented, agency/provider performance is only measurable by the degree to which clients complete the pre-determined fixed number of sessions arbitrarily set by the researcher. Thus, if an agency reports that 80% of their clients completed at least 3 of 5 sessions of an intervention, and only 50% completed all five sessions, the provider could be deemed deficient and could lose funding, even though it is entirely possible, but unknown, that three sessions of intervention is sufficient to achieve viral suppression in that patient population.

Unlike other areas in the universe of behavioral interventions, there are no dose-determining trials to inform HIV treatment adherence interventions. Dose-determination trials have been conducted for psychotherapy in treating schizophrenia [16], depression [17], and adherence counseling for osteoporosis treatment [18]. But there are no dose determination trials for HIV-related behavioral interventions despite HIV demanding high-levels of lifetime engagement in care and treatment adherence. This gap in the evidence-base for HIV treatment engagement and adherence interventions has policy implications that are impeding intervention implementation and scale-up.

Behavioral Intervention Dose Determination Trials

The classic dose-finding scheme for determining optimal dosing in drug studies can be adapted for behavioral interventions and can frame a research agenda for dose-finding trials. Figure 1 offers an adaptation of a common conceptualization for dose-finding in pharmaceutical research, where determining the optimal dose is a function of tolerability (the inverse of toxicity) and treatment efficacy. In drug trials, data on tolerability and efficacy are used to derive a risk–benefit curve. The optimal dose is defined by achieving maximal efficacy with minimal toxicity. In the behavioral intervention context, physiological toxicity is not a relevant concept [14]. However, excessive counseling can cause psychosocial toxicity—exhausting emotions, fostering dependency and diminishing self-efficacy. Overdosing counseling also carries economic costs, wastes resources and overburdens service providers. Behavioral interventionists can determine the minimum effective dose that maximizes the probability of HIV suppression, for example, during the course of the delivering the intervention at the lowest cost/burden. The

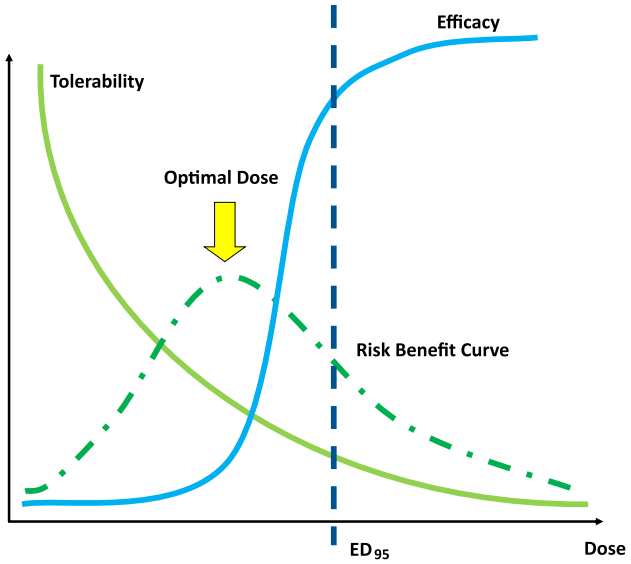

Fig. 1 Classic dose-determination risk benefit curve in drug trials adapted for behavioral interventions. The optimal dose is a function of tolerability and efficacy, with the 95% confidence interval for the effective dose (ED_{95}) defined on the risk–benefit curve

costs of overdosing in behavioral interventions results from expending limited resources, impeding scale-up, and overburdening systems. Statistically, dichotomous outcomes, such as viral suppression, have been a focus in drug development research and are adaptable for behavioral interventions [19]. The minimum effective dose can be determined for a patient population as well key population subgroups. For example, differential dosing can be determined for gender, depression, alcohol and other drug use, food security, and virtually any other known and theorized moderator of adherence outcomes [20].

In the best of worlds, dose finding trials should be included in proofs of concept. For most behavioral interventions, proof of concept trials typically answer questions of acceptability, feasibility, and potential efficacy. Within this context, intervention dose is an obvious and yet overlooked question. Unless dose is determined in the early stages of research it becomes too expensive to determine within the scope of a large-scale efficacy trial. Dose finding trial designs require decisions on the amount of intervention time, number of doses to be tested, dose frequency/spacing, duration of intervention, whether to include an active control, intervention endpoint, etc. Dose-finding trials can be conducted by escalating the number of sessions (dose) until response (adherence/viral suppression) occurs. In a titration design, sessions are titrated to the maximum tolerated dose within participants. In this design, participants all start at a low dose and receive an incrementally higher dose until the maximum tolerated dose is reached. In behavioral research, interventions may become supportive and oriented towards

relapse prevention once clinical outcomes are achieved. However, maintenance and support are different intervention outcomes than efficacy, requiring dose determination trials in their own right. In addition, there is great variability in intervention response, and titration designs offer the opportunity to examine differential response by participant subgroups, essentially the participant characteristic X dose interaction.

In drug development, dosing trials are designed different in oncology and non-oncology settings, as the implications of toxicity, tolerance, and disease progression are unique in oncology [20]. Dose determination designs in non-oncology settings are therefore the most relevant to ART adherence interventions. In addition, not all of the concepts in non-oncology dose finding trial designs are relevant to behavioral interventions. Nevertheless, just as translating concepts from biomedical research to behavioral research with regard to staging clinical trials (Phase I, Phase II, etc.) has proven useful, developing a framework for dose determination in behavioral trials may advance the field.

Dose-Determination Trial Designs for HIV Behavioral Interventions

Several options for designing dose determination trials are available, with some more easily adapted to behavioral interventions than others. For example, a common approach to dose-finding in Phase-I drug development is sequentially raising the dose in successive groups of participants to monitor therapeutic effects and toxicity. This approach to finding the optimal dose essentially balances benefit against risks. In guidance to the pharmaceutical industry for determining dose in support of registering new drugs, the US Food and Drug Administration describes four trial designs [21] which can most clearly be mapped onto behavioral interventions.

Parallel Dose–Response Designs

In these trials, groups of patients are randomized to fixed-doses, with the size of each group determined by an estimate of statistical power. Unless designed as a single-session (one-shot) intervention, the parallel dose–response design could be used for behavioral interventions. Statistical power should include estimates for moderating characteristics (substance use, depression, food insecurity, etc.) and potential combinations of moderators. These designs can also include a placebo control to help interpret results in the event that all groups show a similar slope in response relative to each other. In cases where combinations of interventions may be used, such as adherence counseling and text message reminders, a factorial version of the parallel dose design can be used, such that there may be three levels of counseling dose (3 sessions vs. 5 sessions vs. 7 sessions) and two levels of text message reminders (daily vs. intermittent). A 3×2 design would inform the dose of the combination. However, as is the case in all factorial designs, the sample size escalates to gain enough power to test the interaction effects.

Cross-Over Dose Response Designs

In these trials, individuals are randomized to different intervention doses with increased dose (added sessions) for people who return to baseline after treatment cessation. However, one of the assumptions in a cross-over dose response design is that there are minimal carry over effects between doses, an assumption that does not translate well to most behavioral interventions where early session effects are expected to carry over (e.g., practice and mastery effects). Thus, restarting counseling and adding sessions results in more of an aggregate of intervention than testing a new dose.

Forced Titration Designs

In these designs, all participants move through a series of rising doses. Including a parallel placebo control group allows for a series of comparisons between participants receiving dose-levels with a single control group. In drug trials, forced titration carries a disadvantage is the inability to distinguish increased dose from increased time, a concept that does not map well onto behavioral interventions where cumulative carry-over intervention effects are expected and conceptually relevant to dose. Similarly, concerns about spontaneous improvement and delayed toxicities that can occur with drugs and raise concerns with forced titration do not necessarily apply to behavioral interventions. Thus, forced titration designs may serve behavioral interventions well.

Optional Titration (placebo-Controlled Titration to Endpoint)

Like the forced titration designs, all participants move through a series of rising doses, but in this case the dosing stops with a favorable therapeutic response or an unfavorable outcome. And while physiological toxicity is not a relevant concept in behavioral interventions, that is it seems that no one has died from too much counseling, excessive counseling wastes resources and can carry psychosocial toxicities. Like the designs discussed above, a placebo control group allows for multiple comparisons for subgroups at various levels of dosing. Titration designs require fewer participants than multiple parallel fixed dose designs and can offer clear evidence for effectiveness within and between population subgroups. In drug research, these are often the first dosing trials and they seem particularly well-suited to behavioral interventions.

Dose-Determination Cost-Effectiveness

While concepts of physiological tolerability and toxicity do not translate well to behavioral interventions, one adverse effect of too much behavioral intervention is cost. It is therefore likely that the most useful dose-determination trials for behavioral interventions will address questions of cost. Cost-effectiveness modeling can examine economic considerations associated with counseling dose and how costs change in relation to key population characteristics (e.g., gender, age, substance use, depression, etc.). A simple approach will be to analyze the costs-per-dose from both a provider perspective and from a more comprehensive "societal" perspective [22]. The main difference between these two perspectives is that the societal perspective includes costs to clients, such as phone usage, transportation, child care and other expenses associated with the intervention, whereas the provider perspective omits these costs. The societal perspective also includes the "opportunity cost" of participation, which reflects the foregone earnings or other value that participants place on their time. For example, after estimating the cost of providing a single session (dose), it is possible to assess the costs of multiple sessions, as well as ranges of sessions. Along with dose findings, cost findings can be summarized for specific subgroups, such that results can inform the recommended number of sessions, expected number of sessions completed, and the effective costs. It is also possible to conduct multivariate sensitivity analyses to determine how cost-effectiveness findings might differ with changes to combinations of population characteristics as well as univariate threshold analyses to determine "tipping points" that change findings from cost-effective to not cost-effective or from cost-saving to not cost-saving.

Conclusion

The goal of this Editorial is to raise the issue of how an absence of dose-determination research in HIV behavioral interventions, many of which have been published in *AIDS and Behavior*, impedes interpretation of trial outcomes and their implementation. In an era where so much emphasis is being placed on implementation science to guide the use of efficacious interventions in real world settings, we cannot even answer the most basic questions about how much behavioral intervention is needed to achieve optimal outcomes for whom and what cost. Dose-determination trials for evidence-based HIV behavioral interventions should be a research priority and will be treated with high-priority at *AIDS and Behavior*.

Acknowledgements Moira Kalichman contributed to the conceptualization of psychosocial toxicity and Fig. 1 was created by Ellen Banas.

References

1. Gardner EM, McLees MP, Steiner JF, Del Rio C, Burman WJ. The spectrum of engagement in HIV care and its relevance to test-and-treat strategies for prevention of HIV infection. Clin Infect Dis. 2011;52(6):793–800.
2. Crepaz N, Tang T, Marks G, Mugavero MJ, Espinoza L, Hall HI. Durable viral suppression and transmission risk potential among persons with diagnosed HIV infection: United States, 2012–2013. Clin Infect Dis. 2016;63(7):976–83.
3. Marks G, Patel U, Stirratt MJ, Mugavero MJ, Mathews WC, Giordano TP, et al. Single viral load measurements overestimate stable viral suppression among HIV patients in care: clinical and public health implications. J Acquir Immune Defic Syndr. 1999;73(2):205.
4. Marks G, Gardner LI, Rose CE, Zinski A, Moore RD, Holman S, et al. Time above 1500 copies: a viral load measure for assessing transmission risk of HIV-positive patients in care. AIDS. 2015;29(8):947–54.
5. Iwuji C, Newell ML. Towards control of the global HIV epidemic: addressing the middle-90 challenge in the UNAIDS 90-90-90 target. PLoS Med. 2017;14(5):e1002293.
6. Phillips A, Shroufi A, Vojnov L, Cohn J, Roberts T, et al. Working group on modelling of antiretroviral therapy monitoring strategies in Sub-Saharan Africa sustainable HIV treatment in Africa through viral-load-informed differentiated care. Nature. 2015;528(7580):S68–76.
7. Charania, Marshall KJ, Lyles CM, Crepaz N, Kay LS, Koenig LJ, et al. Identification of evidence-based interventions for promoting HIV medication adherence: findings from a systematic review of U.S.-based studies, 1996–2011. AIDS Behav. 2014;18(4):646–60.
8. Kunutsor S, Walley J, Katabira E, Muchuro S, Balidawa H, Namagala E, et al. Improving clinic attendance and adherence to antiretroviral therapy through a treatment supporter intervention in Uganda: a randomized controlled trial. AIDS Behav. 2011;15(8):1795–802.
9. Haberer JE, Sabin L, Amico KR, Orrell C, Galarraga O, Tsai AC, et al. Improving antiretroviral therapy adherence in resource-limited settings at scale: a discussion of interventions and recommendations. J Int AIDS Soc. 2017;20(1):21371.
10. Shaw S, Amico KR. Antiretroviral therapy adherence enhancing interventions for adolescents and young adults 13–24 years of age: a review of the evidence base. J Acquir Immune Defic Syndr. 2016;72(4):387–99.
11. Centers for Disease C, and Prevention. Compendium of Evidence-Based Interventions CDC; 2019 [Available from: https://www.cdc.gov/hiv/research/interventionresearch/compendium/ma/characteristics.html.
12. Simoni JM, Pearson CR, Pantalone DW, Marks G, Crepaz N. Efficacy of interventions in improving highly active antiretroviral therapy adherence and HIV-1 RNA viral load. A meta-analytic review of randomized controlled trials. J Acquir Immune Defic Syndr. 1999;43(01):S23.
13. Voils CI, Chang Y, Crandell J, Leeman J, Sandelowski M, Maciejewski ML. Informing the dosing of interventions in randomized trials. Contemp Clin Trials. 2012;33(6):1225–30.
14. Voils CI, King HA, Maciejewski ML, Allen KD, Yancy WS Jr, Shaffer JA. Approaches for informing optimal dose of behavioral interventions. Ann Behav Med. 2014;48(3):392–401.
15. Kalichman SC, Kalichman MO, Cherry C, Eaton LA, Cruess D, Schinazi RF. Randomized factorial trial of phone-delivered

support counseling and daily text message reminders for HIV treatment adherence. J Acquir Immune Defic Syndr. 2016;73(1):47–54.
16. Citrome L, Reist C, Palmer L, Montejano L, Lenhart G, Cuffel B, et al. Dose trends for second-generation antipsychotic treatment of schizophrenia and bipolar disorder. Schizophr Res. 2009;108(1–3):238–44.
17. Hansen NB, Lambert MJ. An evaluation of the dose-response relationship in naturalistic treatment settings using survival analysis. Mental Health Serv Res. 2003;5(1):1–12.
18. Cook PF, Emiliozzi S, McCabe MM. Telephone counseling to improve osteoporosis treatment adherence: an effectiveness study in community practice settings. Am J Med Qual. 2007;22(6):445–56.
19. Ivanova A. A new dose-finding design for bivariate outcomes. Biometrics. 2003;59(4):1001–7.
20. Ivanova A, Xiao C, Tymofyeyev Y. Two-stage designs for Phase 2 dose-finding trials. Stat Med. 2012;31(24):2872–81.
21. Administration FaD. Harmonisation International Conference; guidelines availability: Dose-response information to support drug registration. Federal Register: US Government; 1994.
22. Pinkerton SD, Holtgrave DR. The cost-effectiveness of HIV prevention from a managed care perspective. J Public Health Manag Pract. 1998;4(1):59–66.
23. Kurth AE, Spielberg F, Cleland CM, Lambdin B, Bangsberg DR, Frick PA, et al. Computerized counseling reduces HIV-1 viral load and sexual transmission risk: findings from a randomized controlled trial. J Acquir Immune Defic Syndr. 2014;65(5):611–20.
24. Remien RH, Stirratt MJ, Dolezal C, Dognin JS, Wagner GJ, Carballo-Dieguez A, et al. Couple-focused support to improve HIV medication adherence: a randomized controlled trial. AIDS. 2005;19(8):807–14.
25. Kalichman SC, Cherry C, Kalichman MO, Amaral CM, White D, Pope H, et al. Integrated behavioral intervention to improve HIV/AIDS treatment adherence and reduce HIV transmission. Am J Public Health. 2011;101(3):531–8.
26. Hoffmann CJ, Mabuto T, Ginindza S, Fielding KL, Kubeka G, Dowdy DW, et al. Strategies to accelerate HIV care and antiretroviral therapy initiation after HIV diagnosis: a randomized trial. J Acquir Immune Defic Syndr. 2017;75(5):540–7.
27. Johnson MO, Charlebois E, Morin SF, Remien RH, Chesney MA. Effects of a behavioral intervention on antiretroviral medication adherence among people living with HIV: the healthy living project randomized controlled study. J Acquir Immune Defic Syndr. 2007;46(5):574–80.
28. Koenig LJ, Pals SL, Bush T, Pratt Palmore M, Stratford D, Ellerbrock TV. Randomized controlled trial of an intervention to prevent adherence failure among HIV-infected patients initiating antiretroviral therapy. Health Psychol. 2008;27(2):159–69.
29. Gross R, Bellamy SL, Chapman J, Han X, O'Duor J, Palmer SC, et al. Managed problem solving for antiretroviral therapy adherence: a randomized trial. JAMA Intern Med. 2013;173(4):300–6.
30. de Bruin M, Oberje EJM, Viechtbauer W, Nobel HE, Hiligsmann M, van Nieuwkoop C, et al. Effectiveness and cost-effectiveness of a nurse-delivered intervention to improve adherence to treatment for HIV: a pragmatic, multicentre, open-label, randomised clinical trial. Lancet Infect Dis. 2017;17(6):595–604.
31. Milam J, Richardson JL, McCutchan A, Stoyanoff S, Weiss J, Kemper C, et al. Effect of a brief antiretroviral adherence intervention delivered by HIV care providers. J Acquir Immune Defic Syndr. 2005;40(3):356–63.