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Optimizing ART Adherence: Update for HIV Treatment and Prevention

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Abstract

Optimal adherence to antiretroviral therapy (ART) is central to achieving viral suppression and positive health outcomes in HIV-infected individuals. Virally suppressed individuals can also reduce the risk of HIV transmission to uninfected partners. Hence, adherence to ART has become both an HIV treatment and an HIV prevention strategy. However, achieving optimal ART adherence can be challenging, especially over the long term. It is increasingly important for clinicians and researchers to be abreast of the most recent developments in the field as new biomedical approaches to treatment emerge, and as guidelines for the use of pre-exposure prophylaxis (PrEP) are disseminated to providers serving HIV affected populations. Several reviews have described numerous ART adherence interventions that have been developed and/or tested with the most recent review including literature up to 2012. To augment the literature, we present a review of ART adherence interventions from 2013 – present. We included peer-reviewed journals as well as abstracts from two key conferences.

Keywords

HIV; ART; Adherence; Intervention; Review

INTRODUCTION

With the advent of a wide range of treatments for many chronic illnesses, patients' adherence to recommended treatment and care has been an ongoing clinical concern and area of research for many decades [1]. Non-adherence to medications is a limiting factor in the successful treatment of numerous health conditions, including hypertension, diabetes, tuberculosis, and mental illness. Antiretroviral therapy (ART) to treat HIV disease ranks high as a “non-forgiving” treatment regimen compared to many other treatments for chronic

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Compliance with Ethics Guidelines

Conflict of Interest

Reuben N. Robbins, Anya Y. Spector, Claude A. Mellins, and Robert H. Remien declare that they have no conflict of interest

Human and Animal Rights and Informed Consent

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illnesses. Relatively short lapses in medication adherence can lead to the development of viral resistance, compromising the treatment options available to the patient and ultimately the health of the person living with HIV [2–4]. Non-adherence to ART is believed to be the strongest predictor of poor clinical outcomes, including morbidity and mortality for people living with HIV [5–8].

Since the development of effective combination therapy to treat HIV in 1996, there has been a great deal of attention devoted to establishing optimal adherence for people initiating ART and for those already on treatments who demonstrate sub-optimal adherence. ART is an effective HIV prevention strategy resulting in a significant reduction in HIV transmission when HIV positive individuals maintain a low or undetectable viral load [9]. Increasingly, the “test and treat” paradigm, which recommends universal testing and immediate treatment, is being promoted to help curtail the HIV epidemic [10, 11]. Thus, efforts to initiate early treatment for those individuals that test positive are critical to preventing HIV among their sexual partners. To achieve substantial protection, individuals must either have complete viral suppression, always practice safer sex, or preferably both. Viral suppression is attainable through complying with medication dosing. Unfortunately, it is estimated that only 19–28% of HIV-infected individuals in the United States achieve full viral suppression [12, 13, 20]. Furthermore, poor adherence to ART increases HIV infectiousness due to increased viral shedding in the genital compartment [14].

The importance of adherence to ART is not just for those infected with HIV, but also for those at risk for infection. Pre-Exposure Prophylaxis (PrEP) is essentially ART; it contains two commonly used medicines (tenofovir and emtricitabine) that in combination with other medications are used to treat HIV. Strong evidence for the effectiveness of PrEP, to prevent HIV acquisition among those vulnerable to acquiring HIV, through the use of topical PrEP agents in the form of microbicide gels [15] and oral medication [16, 17] has been reported. While not all clinical trials of PrEP have been successful, secondary analyses indicated that when participants’ adherence was high, the drug was highly effective in preventing the acquisition of HIV. Among the trials that failed, it was shown that adherence was very poor [18]. Ultimately it is adherence to these biomedical interventions that predicts desired outcomes, namely the prevention of HIV acquisition.

Thus, despite increased emphasis on developing new pharmacological interventions [19], like PrEP, in the arsenal to combat the spread of HIV, adherence continues to be a lynchpin in providing long-term viral suppression for those already infected and adherence to PrEP offers a viable form of protection for those uninfected and at highest risk for acquiring HIV. Also, adherence to PrEP in clinical trials has been wrought with challenges, leading researchers and health care providers to wonder about the potential impact of intermittent or inconsistent PrEP use on healthy uninfected individuals [15–18].

Increasingly, fiscal resources for health care, in general, and HIV care, specifically, are being limited, therefore it is crucial to prioritize those interventions that have been shown to improve adherence. Research on the barriers to ART adherence has demonstrated that lack of knowledge about HIV-infection and HIV treatment, treatment self-efficacy [21], memory to take one’s medication, and social support to adhere, as well as substance abuse [22],

mental illness [23], food insecurity [24], stigma [25], inconsistent access to healthcare, transportation [26], low income and low education [27] are predictors of poor adherence. This research has given way to studies focused on developing and testing adherence interventions that address one or more of these factors. Meta-analyses of behavioral interventions [28–30] have shown that the most effective interventions used cognitive-behavioral models and shared a core set of psycho-educational components: (1) education about HIV and adherence; (2) teaching self-monitoring skills; (3) identifying adherence barriers; (4) improving problem-solving skills; and (5) reframing treatment beliefs and attitudes.

Chaiyachati and colleagues' "rapid systematic review" of interventions to improve adherence to ART [30] included pre-existing systematic reviews and randomized controlled trials (RCTs) published between 2010 and 2012. Out of 124 studies that met their selection criteria, 86 were RCTs, and more than 20 studies tested the effectiveness of cognitive-behavioral interventions, education about HIV and medication, treatment supporters (e.g., family, friends), directly observed therapy, and interactive reminders (such as mobile phone text messages). They reported that while there was strong evidence that all of these strategies can significantly increase ART adherence in the short-term, several studies failed to produce significant effects, Combination interventions (i.e., those that use more than one strategy to promote adherence) tended to have effects that were similar to those including only a single strategy, and long-term effects on adherence were either difficult to achieve or were not studied.

The first and only Clinical Guidelines for improving entry into and retention in care and ART adherence for persons with HIV was published in 2012 [31]. A panel of 31 medical and behavioral experts reviewed 325 studies that met criteria in accordance with Institute of Medicine Standards for Developing Trustworthy Clinical Practice Guidelines. A total of 39 recommendations were made in 4 domains: 1. clinical monitoring of entry and retention in care; 2. adherence tools; 3. education and counseling; and 4. health system and service delivery interventions. Recommendations for optimizing ART adherence included the following: a) reminder devices and other communication technologies with an interactive component, b) providing education and counseling using specific adherence-related tools, c) providing individual as well as group (including multidisciplinary) ART education and counseling, d) peer support, e) case management services and resources to address food insecurity, housing, and transportation needs, and f) integration of medication management services into pharmacy systems (see original article for more details).

Given the prominent role of adherence to ART in preventing HIV transmission, researchers and clinicians must continue to remain current on recent advances in adherence research. This is especially important for providers serving populations with disproportionately high HIV incidence rates, such as young men who have sex with men (MSM), and African American men in the US [45]. Providers may be called upon to offer PrEP and must be prepared to help ensure patients' adherence to medication. Previous reviews on ART adherence interventions only included studies that were published through 2012. In light of recent medical and behavioral advances, our goal was to review the most recent additions to the literature on studies examining interventions to improve ART adherence or clinical

outcomes (i.e., decreased viral load and increased CD4 cell count) for HIV-infected individuals and improve adherence for those on PrEP from 2013 to the present, as well as to offer insights for the development of future of interventions to improve adherence.

METHOD

A systematic review of the published literature was performed to identify empirical studies of behavioral interventions to promote adherence to antiretroviral therapy (ART), combined ART (cART), highly active ART (HAART) or to Pre-exposure Prophylaxis (PrEP) medication regimens. Studies describing this aim were selected for review if they were published over the past year (between 2013 and 2014), were published in peer-reviewed journals, described outcome data (i.e. not only program description) and were reported in English. The literature search was conducted via Medline (searchable through PubMed), and PsycInfo and SocIndex databases, two online databases in the social and health sciences. Search term categories for the first search included: adherence to anti-retrovirals, compliance with anti-retrovirals, adherence to PrEP, adherence interventions, HIV medication adherence, HIV treatment adherence. This resulted in a total of ten studies that met the criteria. Secondly, we reviewed poster abstracts from two recent conferences: the annual Conference on Retroviruses and Opportunistic Infections (CROI) held in March, 2014 in Boston, Massachusetts, and the 9th International Conference on HIV Treatment and Prevention Adherence, held in June, 2014 in Miami, Florida. Similar to our review of the published literature we searched for poster abstracts that described empirical studies of behavioral interventions to promote adherence to ART, cART, HAART or to PrEP medication regimens, however our search included pilot studies as well as studies that reported preliminary findings.

RESULTS

We identified 10 peer-reviewed journal articles (Table 1) and 11 poster abstracts (Table 2) describing results from both RCT and pilot studies of adherence interventions from 2013 to the present. We also included two recent studies from our group. The interventions reviewed ranged from individual counseling to text messaging to computerized self-administered approaches among various populations, such as youth [32, 33], newly released inmates [34], transgender women [35], and adults with low health literacy [36]. Among those interventions for adults, some had samples that were predominantly African American [32], except for two that were specifically developed for Hispanic and Latino individuals [37, 38]. Among those integrating technological components, one intervention used a self-administered computer program [39], three used text messages [40–42], one was a self-administered ART adherence breathalyzer [43], and another a mobile application [44] for use with smartphones.

Youth

Youth represent a particularly important segment of the HIV epidemic, as in the US, HIV incidence is highest among young MSM [45], and in sub-Saharan Africa, where millions of perinatally infected children will have to spend the entirety of their lives on ART [67]. Among the interventions reviewed for youth, two included families. Multisystemic therapy

(MST) was compared to usual care plus Motivational Interviewing (MI) to improve ART adherence [33] among predominantly perinatally infected youth between 9–17 years of age. Originally developed for youth with conduct disorders [46], MST was adapted for pediatric HIV care to address ART adherence problems. The MST intervention was delivered through home and community based behavioral interventions, and focused on: (a) identifying and addressing youth's individual risk factors, (b) offering interventions for caregivers, (c) providing home-based treatment, and (d) fostering connections to community supports. While participants randomized to MST showed significantly greater decreases in viral load (VL) at 9 months post-baseline compared to the MI group, there were no differences between groups on CD4 and self-report adherence, though CD4 and adherence improved significantly from treatment initiation to study end. Though feasibility and initial efficacy were supported for this MST-based intervention, MST's intensiveness requires tremendous personnel and time resources for providers, as well as the youth and families being treated, and may be difficult to scale-up.

The 10-session VUKA ("Let's wake up" in isiZulu) family program [47], adapted from the CHAMP and CHAMPSA interventions [48, 49] for South Africa, is a family-based behavioral intervention for early adolescents perinatally-infected with HIV to promote positive health. VUKA relies on a cartoon-based story-line that presents adolescents and their families with important information about HIV disease, HIV transmission, HIV treatment and adherence, disclosing one's HIV status, AIDS-related loss and bereavement, coping with HIV, stigma and discrimination and child-caregiver communication, puberty, identifying and developing strategies to promote safe sex, and social support. Pilot RCT results of the VUKA intervention indicated that preadolescents and their families receiving VUKA had significantly greater self-reported ART adherence and caregivers reported significantly greater positive change in discussing sensitive topics with their children than those the standard care group. A larger RCT is underway in South Africa to examine the efficacy of VUKA.

A cell phone support intervention for perinatally and behaviorally infected youth, recruited from the Adolescent Trials Network for HIV/AIDS Interventions, demonstrated that youth with reported ART non-adherence receiving 1–2 calls per day by trained, lay facilitators knowledgeable about HIV treatment showed significantly better improvements in adherence than the control group [32]. This was a small study with 19 youth randomized to receive the cell phone support or standard care. Facilitator initiated support calls consisted of discussing whether the youth had taken his or her medication, as well as encouraging youth to express any issues related to taking ART, problem-solving, and assisting youth in accessing clinic and community resources. Intervention arm improvements in adherence were observed in week 24 and sustained through week 48.

Technology

Over the past several years, great interest has emerged in leveraging technology, such as portable computers, smartphones and tablets, and web-based applications, for the promotion of health behaviors [68–74]. Technology represents an important area of clinical practice and research, as new innovations can increase capacity of resource limited healthcare

settings and enhance health care delivery, as well as promote positive health outcomes. Among the 7 interventions we identified using technology-based strategies, three examined text messaging based ART adherence interventions. Tailored text messaging [40] was shown to be acceptable to adult HIV patients. Viral load significantly decreased and CD4 counts significantly increased among all study participants, while self-reported adherence increased only among the non-adherent patients. Participants received text messages based on self-reported medication adherence (e.g., self-report in the past 7 days, and newly initiated or previously non-adherent). For those who complied with medication regimens messages included, “He shoots! He scores! Great job!” Messages for those non-compliant ranged from 1–3 times per day, while compliant participants received weekly messages. Participants’ weekly self-reported adherence would determine the following week’s text messages. However, the study lasted only 4 months with no long-term follow up. While findings appear promising, this was a small study with no control group, and previous research has shown only limited efficacy for text messaging based interventions [28].

Other text messaging based interventions included bi-directional text messages that included reminders, problem solving, and supportive texts [41] and text messaging for substance using HIV-infected adults [42]. Bidirectional text messaging was found to be feasible given the high rate of cell phone use in the clinic site; ART adherence was not directly measured [41]. Substance using patients in another text messaging intervention showed significantly better self-reported and pharmacy refill estimated ART adherence at 3-month follow-up compared to the treatment as usual group [42]. However, there were no differences in ART adherence between intervention and control groups at 6-month follow-up [42].

Two studies examined novel technology-based interventions. A novel breathalyzer measuring ART adherence (the SMART adherence system) was examined for usability and acceptability [43]. Only 25% of the 12 participants reported they would use the breathalyzer long-term, though 92% said they would use it as part of a study. While an easy to use, immediate result measure of ART adherence could offer patients and providers an important tool; further research on the SMART adherence system is needed. An acceptability study of a mobile application, “app”, for smartphones included appointment reminders, medication reminders, viral load and CD4 tracking, adherence tips, and contact information for health care providers [44]. All nine adult participants thought the app would be useful for adherence.

Two studies examined multimedia computer-based interventions; one was self-administered [39], the other was lay counselor delivered [50]. A pilot test of the self-administered *eLifeSteps* intervention compared to treatment as usual showed that participants in the intervention condition reported higher self-efficacy to adhere to ART than those in the control arm, though there were no differences between groups on self-reported ART adherence rates. The *eLifeSteps* program is a single session, self-paced intervention based on Life Steps [51], which includes videos and a quiz that lasts between 33 to 90 minutes. Content covers information about ART adherence to increase self-efficacy, problem-solving about transportation to appointments, planning for continued access to medications, techniques to communicate with health providers, coping with side-effects, developing a daily medication schedule, problem solving techniques for storing medications, techniques

to cue for pill taking, lessons on how to manage treatment slip-ups/mistakes, and reviews with a quiz.

Masivukeni (“Let’s wake up” in isiXhosa), a multimedia, laptop-based, lay counselor-delivered intervention adapted from SMART Couples [52, 53], demonstrated high acceptability by patients, lay counselors, and clinic staff, as well as feasibility of use in a busy resource-limited, public healthcare setting in the Western Cape Region of South Africa [52]. In a pilot RCT among clinic identified non-adherent adult HIV patients, Masivukeni participants’ pharmacy pill count adherence rates improved by 10%, while standard care (SOC) patients’ adherence declined by 8% at post-intervention, though the difference was not significant [54]. Masivukeni participants also reported significantly more positive attitudes towards disclosure and medication social support, less social rejection, and better clinic-patient relationships than did SOC participants at post-intervention [54]. The six-session Masivukeni intervention uses videos and interactive activities to convey complex information about HIV and HIV treatment, as well as to systematically guide counselors through intervention content. A larger RCT is currently underway in South Africa to test the efficacy of Masivuekni compared to standard adherence counseling among ART-initiators.

Counseling

Nine interventions were based on different counseling modalities (e.g., individual, family and/or group). Results were mixed for these studies. HIV+ Argentinian adults disengaged from treatment and randomized to counseling (education, motivational enhancement and mental health) or standard care showed higher clinic attendance among those who received counseling compared to those in standard care [55]. While self-reported adherence was significantly associated with viral load, no differences between groups were observed. A qualitative study of peer counseling compared to treatment as usual among HIV+ adults virologically failing on ART showed that 90% of those in the peer counseling condition became ART adherent, based on self-report, and remained so at 6 month follow-up [56]. A nurse initiated phone support intervention implemented within the AIDS Clinical Trials Group (ACTG) 384 multicenter trial found no differences in self-reported adherence rates between those randomized to receive the standard adherence phone calls as part of ACTG 384 and those in the site nurse initiated and enhanced support phone call intervention [50]. Participants in the site nurse initiated intervention received calls at 1 to 3 days post ART initiation and then again at weeks 1, 2, 3, 6, 10, 14, 18, 22 and 26 and every 8 weeks thereafter for up to 160 weeks. Findings may have been due to a ceiling effect, as 60% of all participants reported perfect adherence at 32 weeks, with a mean adherence of 98.2%.

Among the counseling-based interventions focused on a specific vulnerable population (e.g., newly released inmates, adults with low health literacy, Hispanic adults, and transgender women) results were also mixed. In a study comparing ecosystem-based versus individual counseling interventions for newly released, HIV+ inmates, intention-to-treat analysis indicated that there were no differences between groups on sexual behavior, and that those in the ecosystem intervention were significantly less likely to be taking ART (by self-report) and to be adherent to meds than those in the individual counseling arm [34]. The ecosystem-based intervention is a counselor delivered intervention that assesses an individuals’

ecosystem, or their external supports, challenges, and resources that comprise their social environment.

Among HIV+ patients who scored less than 90% correct on a test of health literacy were randomized to receive either three sessions of pictograph-guided adherence counseling, standard adherence counseling, or general health counseling. Pictograph-guided adherence counseling was comprised of visual images on a tabletop flip chart the counselor and participant went over together at each session, as well as a pamphlet with minimal words to represent the participant's medication instructions. Those with marginal health literacy showed greater adherence (as measured via unannounced telephone-based pill counts) and lower viral load after receiving the pictograph or standard counseling compared to those who received the general health counseling [36]. There were no differences in adherence between pictograph and standard counseling participants. Those with lower health literacy showed greater adherence after receiving general health counseling than those who received either pictograph or standard counseling.

Two studies examined culturally adapted ART interventions for Hispanic populations. One study found that Hispanic adults randomized to standard care plus culturally sensitive educational information counseling showed significantly higher CD4 counts and HIV knowledge at 6 months post-baseline than those in the standard care only adherence counseling [37]. Adherence was not directly measured in this study. Among HIV+ Latinos of Mexican descent and residing on the U.S.-Mexico border with self-reported non-optimal adherence and depressive symptoms, those randomized to a culturally-adapted cognitive-behavioral therapy for adherence and depression showed a greater drop in depressive symptom scores and greater adherence (as measured by electronic pillbox), and better CD4 counts than those in the treatment as usual group [38].

One study [35] developed a peer led counseling intervention for transgender women and provided women with individual counseling covering medication information, support, and skills building for adherence. Based on electronic pillbox and self-report, 71% increased ART adherence, while 12% showed decreases in adherence. All 12 participants reported high satisfaction with the intervention.

Among HIV+ participants in nine low and middle income sites that were randomized to receive either a partner-based support intervention or usual care for ART adherence, there were no differences between groups at 24-weeks and 48-weeks post-baseline on viral load and adherence (as measured by electronic pillbox) [57]. Partners (e.g., family members, spouses, friends) in the partner-based intervention were trained to implement adherence counseling or to notify medical providers of non-adherence and to observe daily dosing.

Finally, the use of Behavioral Health Consultants (BHCs) embedded in 9 HIV clinics who provide adherence counseling resulted in improvement in retention in care and ART use, based on receipt of prescription and viral load, at one year follow-up [58]. BHCs, usually masters level social workers, served as behavioral health specialists on HIV medical care specialty teams, focused on improving retention, viral suppression, and reducing behavioral health issues. There was no comparison group in this study.

Pre-Exposure Prophylaxis (PrEP)

We identified one recently published abstract that examined an adherence intervention for PrEP and delivered by counselors and pharmacists [59]. Cross-sectional survey and qualitative interviews from 13 clinic sites with clinic staff revealed that counselors were more satisfied with delivering the intervention than pharmacists. Staff thought patients would prefer the counseling intervention that they were trained in. No differences were noted in VOICE participants' adherence pre/post intervention as measured by plasma tenofovir.

CONCLUSION

Optimal adherence to ART for people living with HIV (PLWH) is critical for achieving an undetectable viral load, a hallmark of optimal health. With an undetectable viral load, and safer sex and needle sharing practices (needle-sharing isn't safe by definition), HIV transmission is greatly reduced and the possibility of a world much less affected by the devastation of HIV becomes a possible reality. Yet, maintaining long-term medication adherence, whether for PLWH prescribed ART or healthy individuals on PrEP, is a challenge, as demonstrated in this review. Although there were a number of promising studies, the overall results were mixed, many were very small scale or in the early stages of investigation, and none demonstrated or even examined long term effects – the cornerstone of adherence for those on ART for the duration of their lives. We contend that considerable work, particularly longitudinal research, is needed to address the challenge of life long adherence to treatment.

Corresponding with other health conditions, there is a plethora of HIV-specific research documenting a wide array of adherence barriers, not limited to but including individual level factors (e.g., mental health and substance use problems, motivation, treatment knowledge, attitudes, beliefs and behavioral skills); medication regimen factors (e.g., regimen burden and medication side effects); interpersonal issues (e.g., provider patient communication and social network support); and larger structural issues (e.g., stigma, clinic access, and transportation). Since there is such a wide array of adherence barriers and facilitators that can change over time, it has been challenging to develop and test interventions that are implemented with consistency for all study participants, but that still address the varying specific needs of the individual participants.

In this paper we have focused on the most recent ART adherence interventions, reported in the literature and at two highly important and influential ART adherence and HIV conferences in 2013 and 2014. Since the field is advancing rapidly, it is useful to keep abreast of the latest developments. Of the studies identified in this review, some describe full-scale randomized controlled trials, while others are descriptions of smaller pilot and feasibility studies. The studies identified have targeted a range of populations in terms of age, gender, race, ethnicity, and sexual orientation, and many share common core elements that have been central to adherence interventions that are in the literature from the past several decades, such as increasing patients' knowledge and skills, enhancing social supports, and providing reminder supports for daily adherence. The majority of interventions continue to rely on patient counseling, whether in individual or group settings. There is a

growing emphasis on interventions targeting young people, which is appropriate given the disproportionately higher risk for HIV and need for adherence programs with this population. We also are seeing a growing emphasis on the use of technological supports for intervention delivery, especially with the use of text-messages. With staggering numbers of people living with HIV in low resource settings, often with limited access to counseling resources, the use of technological advances, particularly cell phone technology for text messaging, has been a much needed tool for supporting patient adherence efforts in between health care visits. Finally, only a few of the studies involved adherence interventions to support PrEP, since PrEP has only been recently approved for implementation in community settings.

We were surprised that we did not find recent reports of structural-level adherence interventions in our search since there has been a growing recognition in recent years of the need to intervene at a structural level, be it at the larger society or local community and/or clinic level. While we also would advocate for the development and testing of systemic interventions to improve ART adherence, including linkage and retention in care, we must continue to promote and support adherence behaviors of individuals who are receiving treatment and the providers providing the treatment and care [60]. Further, the needs of individuals vary from person to person and change over time within any individual. Adherence is a dynamic phenomenon [61]. This makes it very challenging to develop and test adherence interventions that are targeted at a population of people, since the specific barriers and facilitators of adherence are likely to differ from person to person receiving the intervention and at any given moment in time. The field is in need of newer methodologies that would allow greater tailoring of intervention activities to meet the range of needs for trial participants. While matching the “diagnosis” with the “treatment” may prove to be helpful for patient adherence, it can be difficult and costly to study with current methodologies, as it may entail very sophisticated, modular and flexible interventions.

A related study design and methodological issue that stems from the reality that study participants assigned to “standard care,” which is often the comparison group to the active intervention being studied in randomized controlled trials, typically will show improvements in the targeted outcomes, thereby limiting the effectiveness demonstrated in the controlled trials [62]. Further, when standard care is variable across studies it is difficult to interpret findings and to generalize to other contexts, especially when standard care is not well-defined in study descriptions [63]. De Bruin and colleagues [62] provide an excellent analysis demonstrating how standard of care comparisons effect trial outcomes and make helpful recommendations for the adherence research field.

While the utilization of technology is exciting and shows promise for efficiency and effectiveness, we would argue that there will continue to be a need for human interaction to optimize adherence over time, particularly for the long-term. This is evidenced in the superiority of two-way text messaging interventions over a one-way (more passive) mode of providing medication reminder supports. Also, we believe that provider-patient communication and support will always be fundamental to good practice and adherence outcomes and advocate for the use of technological supports (i.e., multimedia) to enhance

the capability of providers, including peer and/or lay counselors, particularly in resource constrained settings.

There are a number of limitations to our review. There were only 10 studies that met our criteria and a handful of abstracts from major scientific HIV conferences. The abstracts had limited information and the studies were mixed as to how much information about the intervention itself was presented. A majority of studies as noted were small in scale and 6 months was the longest follow up period. Clearly there is a need for more adherence studies that follow participants for longer periods of time, particularly studies those that focus on the most promising approaches, but also new approaches. To date adherence interventions continue to focus on individual level factors related to self-regulation or use of social support. In studies examining the determinants of medication adherence, mental health and substance use problems continue to be some of the strongest predictors of non-adherence. Only a few adherence interventions actually address psychiatric problems or substance abuse [64–66]. Given that adherence interventions to date have had moderate short-term effects at best, it may be time to begin to address more difficult barriers such as mental health and substance use. Moreover, as noted, structural level interventions and provider-patient level interventions may also be critical to maintenance of long-term adherence. While this review identified some promising ART adherence interventions, challenges to long-term adherence and adherence research remain. Thinking outside the usual box may be critical to changing this course.

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Table 1

ART Adherence Interventions from Peer Reviewed Journals 2013–2014

Study	Type of Intervention	Population/Sample	Design	Measures of Adherence	Findings	Limitations
Belzer ME, Naar-King S, Olson J, Sarr M, Thornton S, Kahana SY, et al. (2013)	Cell phone support	Youth and young adults/37 participants (62% male/70% AA) Behaviorally infected.	RCT	Self report Viral load	Adherence higher in intervention group and VL lower during intervention and at 24 weeks post.	Small sample size, short-term follow up, no confirmation for self-report (e.g., pill counts).
Castro JG, Waldrop-Valverde D, Valverde EE. (2013)	Educational intervention (2 3hr. modules)	400 Hispanic adults in Miami	RCT	CD4 cell counts	Interaction effect b/w HIV knowledge and intervention. CD4 counts sig. higher among those with higher HIV knowledge at 6 mos. post.	CD4 count may not be a result of medication adherence. Selection bias. Most were Cuban-Americans.
Robbins GK, Testa MA, Su M, Safren SA, Morse G, Lammett S, et al. (2013)	Telephone call support	333 patients initiating ART	RCT	Self report	Phone calls did not impact self-reported adherence (no diff b/w control and experimental groups)	Self-report, adherence was high to begin with
Kalichman S, Cherry C, Kalichman MO, Amaral C, White D, Cruess D, et al. (2013)	Pictograph-guided adherence skills building counseling	Limited literacy US adults/446 men and women	RCT (3 arm) (1.intervention; 2.standard adherence counseling; or 3. general health info.)	Un-announced pill count Viral load	Those with marginal health literacy showed greater adherence and lower VL with pictograph and standard counseling, those with lower health literacy showed greater adherence with general health info.	Study did not account for other contextual factors, short-term follow up.
Lewis MA, Uhrig JD, Bann CM, Harris JL, Furberg RD, Coomes C, et al. (2013)	Text messages	52 MSM (33% Black, 44% white, 23% other, 33% Hispanic)	Proof-of-concept study – all participants received text messages	Self report CD4 counts Viral load	Participants receptive to text messaging intervention. Self reported adherence improved among participants who began as non-adherent.	Rigorous testing needed (i.e., randomization). Study didn't account for other contextual factors to explain findings, small sample.
Claborn KR, Leffingwell TR, Miller MB, Ellen Meier E, Stephens JR. (2014)	Computer based intervention to promote adherence.	92 men (82.5% men) and women (16.5%)	RCT	Self report	Participant in experimental condition reported higher self-efficacy to adhere-adherence diffs were nonsignificant.	Short-term follow up, cannot infer causality, small sample, few women in study.
Letourneau EJ, Ellis DA, Naar-King S, Chapman JE, Cunningham PB, Fowler S. (2014)	Multi-systemic therapy	Youth (N=34), most perinatally infected.	Pilot RCT- feasibility and initial efficacy	Viral load	Feasibility and initial efficacy were supported for MST and not for the usual care + MI condition.	Small sample size, overrepresentation of AA and perinatally infected participants, self report.
Reznick OG, McCartney K, Gregorich SE, Zack B, Feaster DJ. (2013)	Counseling intervention	Inmates being released (2 prisons and one jail) (N=151)	RCT	Self report	Ecosystem intervention did not improve adherence.	Ecosystem intervention not applied as intended due to lack of support members and lack of connections due to repeated incarcerations in this population.

Study	Type of Intervention	Population/Sample	Design	Measures of Adherence	Findings	Limitations
Robbins RN, Mellins CA, Leu C, Rowe J, Wame P, Abrams E, et al. (in press)	Multimedia computer-based, lay counselor-delivered intervention to promote adherence	55 non-adherent South African adults (66% female)	RCT	Pharmacy pill count and self report	Pharmacy pill count adherence rates improved by 10% for experimental condition participants and declined by 8% for control. Experimental participants reported significantly more positive attitudes towards disclosure and medication social support, less social rejection, and better clinic-patient relationships than controls. This study offers preliminary evidence that multimedia, computer-based technology can help lay counselors offer better adherence counseling than standard approaches.	Study conducted at only one clinic site and with a small sample, thus findings cannot be generalized. Pharmacy pill count data were not available on all participants. Study did not assess long-term effects.
Bhana A, Mellins CA, Petersen I, Alicea S, Mveza N, Holst H, et al. (2014).	Family based counseling- 10 sessions- delivered by lay counselors	65 South African preadolescents (approximately one half females) aged 10–13 years and their families. Perinatally infected.	RCT	Self report	Participants in experimental condition improved in mental health, behavior, HIV treatment knowledge, stigma, communication and adherence to medication. This lay counselor-delivered family based counseling intervention shows promise for HIV + preadolescents.	Self-reported adherence measures, small sample size, selection bias, short-term follow up.

Table 2

ART Adherence Interventions from Conference Abstracts 2013–2014

Study	Type of Intervention	Population/Sample	Design	Measures of Adherence	Findings	Limitations
9th International Conference on HIV treatment and Prevention Adherence						
Jones D, Bofill L, Arisiegui I, Mattioli I, Ceccini D, Sued O, et al.	Counseling intervention	Men and Women in Argentina N=60	RCT	Self report Viral load	Preliminary findings show that attendance to clinic was higher in intervention group.	Small sample size, short-term follow up.
Enriquez M, Hart K.	Peer facilitated counseling	Adults (N=20)	Qualitative descriptive (part of RCT)	Self report	90% participants randomized to experimental condition (n=9) became adherent at 6 mo. follow up.	Small sample size, self-report adherence measure.
van der Straeten A, Mayo A, Brown E, Amico KR, Cheng H, Laborde N, et al.	Counseling training	Counselors and pharmacists (N=75) at 13 sites and participants in VOICE trial (N=365)	Cross sectional survey and qual. interviews	Plasma TFV	Counselors were more satisfied with intervention than pharmacists. Staff thought patients would prefer intervention. No differences were noted in adherence pre/post intervention for participants.	No longitudinal assessments.
Rana A, van den Berg J, Lamy E, Beckwith CG.	Texting intervention – reminders	Adults (N=32) at Miriam Hospital Clinic	Pilot test- feasibility	None	Use of bi-directional text messaging is feasible at the clinic	No adherence measure. Small sample.
Ingersoll K, Dillingham R, Reynolds G, Freeman J, Hosseinbor A, Hetteema J.	Text messaging	Substance using adults (non-urban). N=63	RCT (feasibility and impact)	Self report Pharmacy refill	Significant improvements Text condition in adherence, engagement and substance use at 3 mo. Follow up – at 6 mo. All measures returned to baseline levels.	Small sample size. Limited adherence measures.
Dennis D, Abrams L, Morey T, Melker R.	SMART adherence system- breathalyzer for HAART	Adults N=12	Usability evaluation	Mini-gas chromatograph	Only 25% reported they would use it long-term.	Small sample size, short term follow up.
Schneider MP, Rotzinger A, Maestralli D, Bugnon O, Cavassini M, Parienti JJ.	Counseling and electronic pill container	Swiss adults (N=430)- 200 attended program	Retrospective cohort study	HIV RNA	Intervention group was more likely to be retained in treatment-no statistically significant differences in HIV RNA.	Limited adherence measures, retrospective study.
Sevelius J, Johnson M, Saberi P.	Peer led counseling	Transgender women (n=19)	Intervention development	MEMS Self report	71% increased ART adherence, 12% declined.	Small sample size, limited adherence measures, no test of intervention.
Teti M, Gerkovich M, Farnan R.	Photo-story tool	Adults (n=16) low income mid-west	Qualitative	None	Photostories are feasible to help adults talk about adherence	No adherence measures, small sample size, selection bias.

Study	Type of Intervention	Population/Sample	Design	Measures of Adherence	Findings	Limitations
Lehrman S, Evans E, Brady K, Terrell C.	Behavioral Health Consultants embedded in clinics- counseling	Adults (N=471) enrolled in BHC services	Survey (baseline and follow up)	Receipt of prescription Viral load	BHC services resulted in improvement in retention in care and ART use.	Short-term follow up.
Green K, Jones R, Ortiz-Ricard A.	Mobile application	Adults (N=9)	Pilot test-interviews	None	All participants thought application would be useful for adherence.	Small sample, no adherence measure, no control group, no follow up.
Conference on Retroviruses and Opportunistic Infections						
Gross R, Zheng L, La Rosa A, Sun X, Rosenkranz S, Cardoso-Wagner S.	Partner based support intervention	Adults with willing support partner (N=129 intervention, 128 control)	RCT	Partner observation MEMS HIV RNA	Virologic failure experienced in 19% in experimental vs. 13% in control (n.s.). MEMS adherence high in both groups. No intervention effect on adherence or viral load.	Short term follow up.