Interventions to improve medication adherence in adolescents with HIV: a systematic review and meta-analysis

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ABSTRACT

As of 2017, 1.8 million people living with HIV (PLWH) were adolescents between ages 10 and 19, accounting for 5% of all PLWH and 590,000 people between the ages 15 and 24 were newly infected with HIV. Between 2004 and 2011, AIDS-related deaths increased 50% among adolescents, and optimal adolescent adherence to antiretroviral treatment (ART) is estimated at only 62% of adolescents worldwide. While there have been great strides toward achieving the UNAIDS 90-90-90 goals, adolescents remain a group lacking appropriate resources and research to achieve these. This review analyzes current interventions aimed toward increasing adolescent ART adherence. Systematic searches of EMBASE, PubMed and PsycINFO were performed using the keywords 'adolescent HIV medication adherence interventions'. The Gain Score effect size was calculated for studies reporting the Cohen's d and variance to include both prestudy and poststudy values. A random-effects model analyzed intervention significance. Authors were contacted to obtain additional data values and study clarification. Twelve studies met inclusion criteria for meta-analysis. There were no significant differences seen between control and intervention groups in medication adherence ($z=-1.4714$, $p<0.1412$), viral load ($z=-0.1946$, $p<0.8547$) or CD4+ lymphocyte count ($z=0.2650$, $p<0.7910$). There was no significant difference between studies in increasing medication adherence. Results indicate that interventions did not improve medication adherence in adolescents with HIV. However, the paucity of quantitative research available speaks to a need for more quantitative intervention studies and standardization of measures of intervention efficacy.

INTRODUCTION

Adolescence represents a time of great change both physically and psychosocially. These changes have been shown to have profound effects on those with chronic illness, with adolescents living with HIV (ALWH) showing decreased adherence to treatment and increased morbidity and mortality.[1 2] Additionally, adolescent patients infected with HIV face difficulties accessing care and must navigate the complexities of the child-caregiver relationship.[3] Finally, the transition from adolescent to adult care is fraught with challenges.[4 5] For antiretroviral therapy (ART) to work effectively with successful outcomes, a high level of adherence must be achieved, varying between 80% and 95% depending on the specific medications being used.[6 7] However, worldwide, only 62% of adolescents on ART therapy achieve an adherence rate of at least 85%.[8 9] With 1.8 million HIV-infected adolescents in 2017 and 50% of AIDS-related deaths occurring in adolescents, non-adherence remains the single most significant challenge in ALWH.[10]

Adolescents face many barriers to adherence. One of the most commonly reported barriers among adolescence and their caregivers is forgetting to take the medication due to busy schedules or complex treatment regimens.[5] Additionally, patients cite "taking it reminds me of HIV" and 'worried that someone will find out' as behavioral and cognitive factors. Others reported they felt they did not need to take medications as they stay healthy without them or that they are still sick despite therapy.[11] Additionally, lack of institutional support has created a gap in the care of ALWH. Much of this group's vulnerability has been attributed to structural and socioeconomic inequalities, failures in protection, limited sexuality education and lack of high-impact HIV and sexual reproductive services.[9] In low-income and middle-income countries, only 30% of boys and 19% of girls are able to name two major means of HIV transmission.[12]

Despite this clear problem, there is a paucity of systematic reviews with quantitative meta-analysis that analyze the effectiveness of HIV adherence interventions in adolescents. In recent years, there have been systematic reviews addressing this topic, such as the reviews performed by Ridgeway *et al* in 2018 and Casale *et al* in 2019, but they lack a quantitative meta-analysis.[13 14] Meta-analysis has been performed on interventions addressing HIV adherence interventions in adults, such as the study done by Kanters *et al* in 2017, but given the unique circumstances and challenges that affect adolescents' adherence, a meta-analysis targeting that specific demographic is warranted.[15]

While there have been great strides toward achieving the UNAIDS 90-90-90 initiative, adolescents remain a group lacking appropriate resources, further expressing the importance of adolescent HIV-focused research.[16] This review looks to synthesize and analyze current interventions through statistical analysis of medication adherence, viral load and CD4 count, with the goal of prompting and directing further research.

METHODS

Search strategy

We conducted a systematic review and meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[17] To search for relevant studies, we used the databases PubMed, PsycINFO and EmBASE. For each database, we searched the keywords 'adolescent HIV medication adherence interventions'. These keywords were entered in directly, without the use of Boolean search operators. These searches were conducted June through August of 2018.

Inclusion criteria

Studies were included in the review if they (1) were published in peer-reviewed journals, (2) were experimental studies with treatment and control groups, (3) included participants who have either congenital or acquired HIV, with a mean age between 12 and 24 years, (4) were published from 2000 to 2018, (5) were written in English, (6) assessed technological, community-based or behavioral interventions and (7) measured at least one of the following outcomes: viral load, CD4+ count or medication adherence.

Data abstraction

For each citation garnered from the search, title and abstract were evaluated for possible relevance to our review. For those deemed possibly relevant to our review, the full article was reviewed, and if it met our inclusion criteria, it was included in our review.

Across the three databases used, our initial search garnered 9513 citations. Of these 9513 citations, 573 were duplicates and thus were removed. The remaining 8940 were screened at the title and abstract level. Of these 8940, 8881 were excluded because they did not meet the aforementioned inclusion criteria, and 59 were assessed at the full-text level for eligibility. Of those 59 assessed at the full-text level, 47 were excluded. Of these 47, 15 were excluded because the study did not include a control group, 6 were excluded because the average subject age was outside of the age range defined in our inclusion criteria, and 26 were excluded because they provided inadequate measures (for the purposes of our meta-analysis, we only included studies that reported Cohen's d or OR values).

This final set of exclusions yielded 12 studies that were included in our systematic review and meta-analysis. Figure 1 indicates this process visually.

Outcome variables and data analysis

The outcome of interest was medication adherence. Due to the variety of measures used across studies, three were chosen for assessment—viral load (7 studies), CD4 count (4 studies) and self-reported medication adherence (10 studies). The directions of intervention effect were inconsistent in measurements. Separate meta-analytic models were built for each of measurements to minimize the measurement bias and heterogeneity.

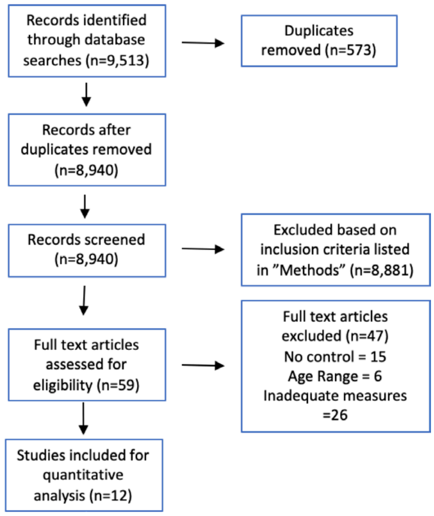

Figure 1 Flow chart of systematic review.

The primary summary statistic was the Cohen's d with SE directly extracted from the pretest-post-test-control group design studies in which the standard mean pre-post change in the intervention group minus the mean pre-post change in the control group was divided by the pooled pretest SD.[18] Additional calculation was required if the study reported means and SD only. Studies reporting the OR and variance were converted to Cohen's d.[18 19]

Fixed-effects, mixed-effects and random-effects models were used to calculate summary effect size for each of three different measures. The results of the random-effects models that produced significantly better model fits were reported in this. The statistical software R was used for all data analyses (V.3.5.0; The R Foundation for Statistical Computing, Kansas, USA).[20 21]

RESULTS

Study characteristics

Twelve studies, which were pretest-post-test design with control group, were included in the final meta-analysis. Of the 12 studies, 3 were categorized as being technological interventions, using text messaging, call reminders or computer programs. Four studies involved community-based interventions, encompassing HIV support groups, family outreach programmes, social outreach or a multisystem approach. Five studies were classified as behavioral interventions, using motivational interviewing, cognitive behavioral therapy, empowerment or mindfulness and stress reduction sessions (table 1).

The influence of different interventions on outcome measures using a one-way analysis of variance (ANOVA) test was not significant (p=0.642). Nonetheless, a more conservative approach applying the random-effects model (the DerSimonian and Laird method) was chosen for all analyses because of the anticipated heterogeneity by the intervention types as well as different studies.

Table 1 Studies included in final meta-analysis

Study	Year published	Intervention type	Sample size	Control group	Intervention group	Outcomes measured
Belzer *et al*[28]	2014	Technological	37	18	19	SR-MA, VL
Bhana *et al*[22]	2015	Community based	65	32	33	SR-MA
Brown *et al*[33]	2016	Behavioral	32	15	17	VL, CD4
Bouris *et al*[31]	2017	Behavioral	98	45	53	SR-MA, VL, CD4
Cluver *et al*[29]	2016	Community based	1059	921	138	SR-MA
Devila *et al*[24]	2012	Community based	174	126	48	SR-MA
Garofalo *et al*[26]	2015	Technological	105	49	45	SR-MA, VL
Kaihin *et al*[23]	2016	Behavioral	46	23	23	SR-MA
Letourneau *et al*[25]	2012	Community based	34	10	24	SR-MA, VL, CD4
Naar King *et al*[27]	2009	Behavioral	186	92	94	VL
Naar King *et al*[32]	2013	Technological	70	37	33	SR-MA, VL
Webb *et al*[30]	2017	Behavioral	72	34	38	SR-MA, CD4

CD4, CD4 count; SR-MA, self-reported medcation adherence; VL, viral load.

Medication adherence

Ten studies reported medication adherence.[22–31] Of the 10 studies, 1 used pill count, 1 used number of doses missed, 1 used visit constancy, 4 used the Visual Analog Scale and 3 used self-reported medical adherence. No significant intervention effects were observed for medical adherence with a summary result of −0.0945 (95% CI −0.2204 to 0.0314; p=0.1412) (figure 2).

The test for heterogeneity showed an I^2 of 0%, and p value of 0.0540, which indicated no detectable heterogeneity of the results. There was no evidence of systematic publication bias on inspection of the funnel plot as well as on Egger's test (p=0.4049).

Viral load

Seven studies reported viral load.[25–28 31–33] Six of seven studies reported viral load as mean log10 viral load and one study reported viral load in copies/mL. All studies collected viral loads at various time points throughout the study, however effect size was calculated using the difference in pre-intervention viral load and post-intervention viral load. Viral loads taken during the intervention period were not included in the analysis.

The average effect size was not significant, d=−0.0275, 95% CI −0.3041 to 0.2492, p=0.8547, suggesting that the interventions are not associated with the level of viral load (figure 3). The test for heterogeneity showed an I^2 of 3.11%, and p value of 0.5310, which indicated no heterogeneity of the results. Furthermore, the funnel plot and Egger's test suggested no evidence of publication bias (p=0.0176).

CD4 count

Four studies reported CD4 counts.[25 30 31 33] Of the four studies, three reported absolute CD4 count and one reported number of patients with CD4 counts >200. The results indicated that there was no significant effects of interventions on CD4 count with the average effect size of 0.0337 (95% CI −0.2152 to 0.2825, p=0.7910) (figure 4). The test for heterogeneity showed an I^2 of 0%, and value of 0.8707, which indicated no heterogeneity. There was no evidence of publication bias on inspection of the funnel plot analysis and on Egger's test (p=0.4919).

DISCUSSION

While there have been great strides to increase testing among adolescents and the promotion of preventative strategies, those already infected continue to face many challenges. Currently, ALWH face many barriers, including feelings of isolation, low socioeconomic status, stigma and misperceptions of HIV.[33] This study examined interventions aimed at reducing these barriers and increasing medication adherence, in the hopes of providing guidance for future research.

However, after extensive review of available literature, there was no significant difference between control and

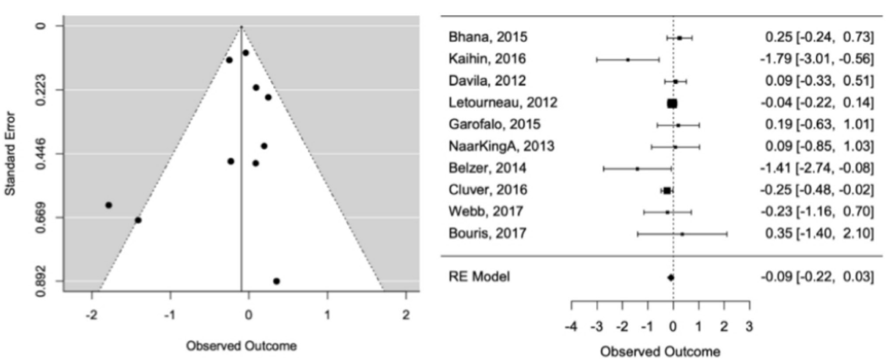

Figure 2 Medication adherence: funnel and forest plot for the random-effects meta-analysis of intervention effects.

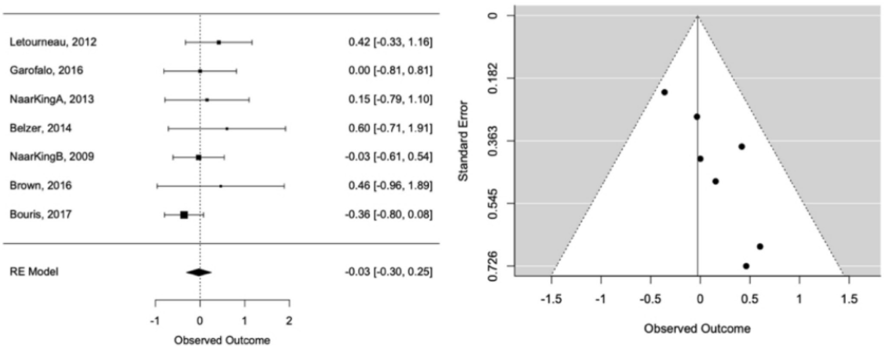

Figure 3 Viral load: funnel and forest plot for the random-effects meta-analysis of intervention effects.

intervention groups on meta-analysis. The lack of significance points to the difficulties of running the meta-analysis and a need for a more standardized reporting system. Despite a plethora of studies reporting on medication adherence in adolescents, few studies met the criteria for inclusion in the analysis, and most studies do not report quantitative results capable of meta-analysis, limiting the power of our meta-analysis. Of the studies included, various statistical values were used to determine intervention efficacy and this variability added difficulty to the process. If studies used a standardized metric to determine intervention success, it is possible the meta-analysis would have been less cumbersome and yielded more reliable data.

In an effort to determine the most efficacious intervention focus, we also analyzed the effects of different intervention types. The one-way ANOVA showed there was no significant difference between intervention types; however, the community-based interventions were shown to be slightly more efficacious than technological-based and behavioral-based interventions. This would suggest that interventions focused on HIV support groups, family outreach programmes, social outreach or a multisystem approach would be more valuable in addressing medication adherence in future studies.

Our study was limited by small sample sizes of many of the eligible reports and the lack of uniform outcome measurement, which in turn limited the potential to identify significant effects on adherence. Nevertheless, our findings were remarkably consistent across intervention types, including mixed interventions. In addition, adherence metrics differed across studies, which was why we tried to include studies that reported adherence and viral load and/or CD4+ count. The majority of the studies in our meta-analysis did so; however, four of our studies Bhana 2013,[22] Kaihin 2014,[23] Davila 2012[24] and Cluver 2016[29] only measured adherence.

As ART options have evolved over the course of the study period, studies included in this analysis enrolled subjects receiving different regimens; however, almost all studies were conducted in the era wherein single-tablet, fixed-dose regiments were widely available. All but one of the studies included in this analysis enrolled both perinatal and behaviorally infected adolescents, making it impossible to address potentially different reasons for poor adherence. Several important differences between perinatally and behaviorally infected adolescents should be considered in the development of adherence plans. Perinatally infected youth are more likely to be in advanced stages of HIV disease, with opportunistic infection risk requiring prophylaxis or treatment, more likely to have multidrug-resistant virus, more complex combination ART (cART) histories and more likely to suffer physical and developmental disabilities. As a result, this group of young people are at higher risk of transmitting HIV to offspring and of suboptimal immune response. In contrast, behaviorally infected youth are more likely to be in early stages of HIV disease, with higher CD4+ count and fewer opportunistic complications, less likely to manifest cART resistance, and so are able to benefit from simpler cART regimens. In addition, this group suffers fewer physical and developmental delays, and less risk of perinatal transmission. However, as noted previously, almost all studies were conducted at a time wherein STR were widely available for treating both populations of ALWH.

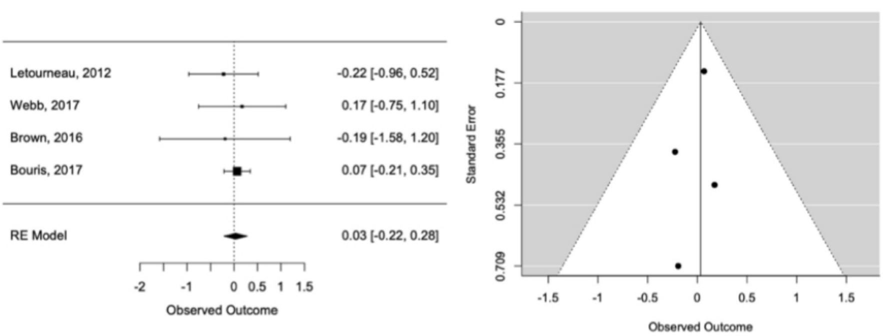

Figure 4 CD4 count: funnel and forest plot for the random-effects meta-analysis of intervention effects.

The most impactful limitation to our analysis was the lack of standardized measures for assessing medication adherence and statistical significance. Measures of adherence analyzed in this study include self-reported adherence, viral load and CD4 count. Further complicating the analysis, five different metrics were used across the studies included to determine medication adherence. Similarly, studies within each intervention subtype assessed the efficacy of a wide variety of tools and programmes. Consequently, if one intervention type was statistically more efficacious than any other, additional data and analysis would be needed to determine the potential parameters for a successful programme. Additionally, the lack of studies and quantitative data, small sample sizes and lack of controlled clinical trials greatly limited our meta-analysis.

Thus, in looking forward to future projects within the field of adolescent HIV, we would suggest studies report data that can be used to estimate the effect size for each study. For example, for the Cohen's d the pre-post mean and SD would allow for estimation of effect size and use in a meta-analysis. This would allow for a more rigorous analysis of intervention efficacy. In addition to more standardized outcome reporting, more studies focused on the needs of adolescents and specific subgroups such as LGBTQ and minority groups are needed to be done.

CONCLUSION

In the USA alone, adolescents comprise 21% of new diagnoses in 2017.[34] Adequate adolescent ART adherence is estimated at only 62% of adolescents worldwide.[35] This study sought to provide insight into the efficacy of interventions aimed at increasing medication adherence. After rigorous meta-analysis, we found no significant difference between control and intervention groups or between intervention types. The difficulties of running the meta-analysis pointed to a need for more quantitative data on intervention outcomes as well as a more standardized reporting system. Our comparison of intervention types found community-based interventions were slightly more effective than technological-based and behavioral-based interventions, but this difference was not statistically significant. The UNAIDS 90-90-90 initiative is aimed at 90% of those with HIV knowing their status, 90% with HIV on ART and 90% virally suppressed.[16] However, without more rigorous and comprehensive studies addressing medication adherence in ALWH, it will be difficult to accomplish this goal. It is our hope that this meta-analysis provides direction on this front.

Contributors SA designed the study selection criteria and search keywords, performed the literature search, drafted the initial manuscript, performed data analysis and reviewed and revised the manuscript. BA and DS designed the study selection criteria and search keywords, performed the literature search and reviewed and revised the manuscript. YSL designed the data analysis and aided in carrying out the analysis, and reviewed and revised the manuscript. JSC conceptualized and designed the study, coordinated and supervised the process and reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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