**Appendix D. Medication Adherence Intervention Summary Evidence Tables**

| First Author, Publication Year, Location | Review Type  (Quantitative/Qualitative) | Target Population | Type of included primary studies, Search period (yr),  # of included primary studies, Sample size | AMSTAR score (range 1-11),  Rating | Adherence Measurement | Interventions Included | Effect Sizes  (NA if narrative systematic review) | Conclusions | Research gaps identified |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Technology Interventions | | | | | | | | | |
| [Amico (2015)](https://www.ncbi.nlm.nih.gov/pubmed/?term=Evidence+for+technology+interventions+to+promote+ART+adherence+in+adult+populations%3A+A+review+of+the+literature+2012-2015)  US and Non-US | Qualitative Synthesis | PWH aged 20 years and older | RCT  2013 – 2015  K=13  N=NR | 5  (medium) | Adherence:  NR  Biologic:  CD4 cell count, viral load | Technology delivered ART adherence intervention | NA | 4 of 13 studies observed stat sig improvements in both adherence and VL or CD4 count.  3 of 13 studies observed stat sig improvements in adherence only.  2 of 13 studies with shorter follow-up (~1 month) observed non-significant improvements in adherence.  4 of 13 studies observed no effect.  Vast majority of interventions had a direct effect or trend on adherence and many had effects on biological outcomes.  Computer software and Internet websites were not consistently effective.  Mobile phone message using interactive texts, and intensive phone-delivered counseling were consistently effective. | More assessment by electronic dose monitoring or ecological assessment strategies  Key populations (e.g., substance users, expecting mothers, sex workers)  Trials examining longer periods of adherence |
| [Claborn et al. (2015)](https://www.ncbi.nlm.nih.gov/pubmed/26327935)  US and Non-US | Qualitative Synthesis | PWH | RCT, non-RCT  2011-2015  N=6  K=NR | 9  (high) | Adherence:  self-report, MEMS  Biologic:  viral load | Computer-delivered interventions that can be completed at clinic or patient’s home | NA | 3 of 6 studies observed statistically significant improvements in adherence; for 2 studies the effect was borderline significant  1 of 2 studies using MEMS caps to measure adherence observed significant improvements.  1 of 3 studies measuring viral load (with a cutoff of >400) observed a significant improvement (p=0.02) but not when using a cutoff of >48. | Longitudinal studies that examine dose response  Cost-effectiveness studies  Fidelity to treatment protocols |
| [Finitsis et al. (2014)](https://www.ncbi.nlm.nih.gov/pubmed/?term=text+message+intervention+designs+to+promote+adherence+to+antiretroviral+therapy+a+meta-analysis+of+randomized+controlled+trials)  US and Non-US | Quantitative Synthesis (meta-analysis) | PWH | RCT  1990 - 2013  K=8  N=1,463 | 11  (high) | Adherence:  pill count  electronic drug monitoring device  pharmacy refill  Biologic:  CD4 cell count, viral load | Mobile phone text messaging | Mobile phone messaging effective at improving adherence (OR = 1.39, 95% CI: 1.18-1.64)  Studies that measured adherence by self-report, viral load, and biological outcomes achieved statistical significance.  Larger effects observed when messaging interventions were (1) not sent daily, (2) supported bidirectional communication, (3) included personalized message content, and (4) were matched to participants’ ART dosing. | Text messaging interventions were effective at improving HIV outcomes.  Less than daily frequency that is individually timed, tailored, and designed to evoke a reply are most effective | Methods to optimize efficacy of text messaging interventions |
| [Gentry et al. (2013)](https://www.ncbi.nlm.nih.gov/pubmed/?term=Telephone+delivered+interventions+for+reducing+morbidity+and+mortality+in+people+with+HIV+infection)  US and non-US | Quantitative Synthesis  (meta-analysis) | PWH | RCT and controlled BA  1980-2011  K=6  N=1,381 | 11  (high) | Adherence: pill counts, electronic monitoring, medical records, self-report: medication diaries  Biologic:  viral load, CD4+ count | Voice landline and mobile telephone delivered interventions | Telephone interventions did not improve medication adherence (SMD 0.49, 95% CI  -1.12 to 2.11). (n=3 studies)  3 additional studies reported favorable effects on adherence.  3 studies assessed virologic outcomes, but they did not observe improvements. | Although some evidence support telephone interventions, meta-analyses on adherence outcomes were not significant. Additionally, little evidence that telephone interventions improve virologic outcomes. | Interventions in developed and developing settings  Economic outcomes  Adverse events |
| [Horvath et al. (2012)](https://www.ncbi.nlm.nih.gov/pubmed/22419345)  Non-US  (Kenya) | Quantitative Synthesis (meta-analysis) | Adult PWH | RCT  1980-2011  N=2  N=NR | 11  (high) | Biologic:  Viral load suppression | Mobile phone text messaging | Any weekly text-messaging (i.e. whether short or long messages) was associated with a lower risk of nonadherence  at 48-52 weeks (RR 0.78, 95% CI 0.68 to 0.89).  The effect of short weekly text-messaging on nonadherence was also significant (RR 0.77,  95% CI 0.67 to 0.89) | High quality evidence from one trial that weekly mobile phone text-messaging is efficacious in improving HIV viral load suppression. | Large RCTs conducted in adolescents and high-income countries |
| [Pellowski & Kalichman](https://www.ncbi.nlm.nih.gov/pubmed/?term=Recent+advances+(2011-2012)+in+technology-delivered+interventions+for+people+living+with+HIV) (2012)  US and Non-US | Qualitative Synthesis | PWH | RCT and non-RCT  (2011-2012)  K=12  N=NR | 5  (medium) | Adherence:  pill counts, MEMS cap,  self-report  Biologic:  viral load, CD4 cell count | Cell Phone Based; SMS/Text Messaging Interventions; Computerized Interventions | NA | 7 of12 interventions revealed significant effects on adherence rate (2 of 12 significant for viral load) | Evidence for emerging trends in the research literature regarding electronically based behavioral interventions for people living with HIV/AIDS |
| [Wise & Operario (2008)](https://www.ncbi.nlm.nih.gov/pubmed/18462071)  US and Non-US | Qualitative  Synthesis | PWH | RCT, non-RCT  (through May 2006)  K=8  NR | 6  (medium) | Adherence: electronic monitoring, pill counts, self-report, pharmacy refill  Biologic:  CD4 cell count, viral load | Electronic reminder devices | NA | 4 of the 8 included studies that examined ERD as a stand-alone adherence strategy observed improved ART adherence.  When combined with other intervention strategies, 5 of the 7 studies reported that ERD was effective | Cost-effectiveness of ERD  ERD interventions in subpopulations such as youth, women, new or switching therapeutic regimens, with memory impairment, resource poor settings |
| Behavioral Interventions | | | | | | | | | |
| [Hill et al. (2012)](https://www.ncbi.nlm.nih.gov/pubmed/22292452)  US and Non-US | Qualitative Synthesis | PWH | RCT  1990-2010  K=5  N=NR | 8  (High) | Adherence: self-report,  electronic monitoring,  pill counts  Biologic:  viral load,  CD4+ count | Motivatio-nal Interviewing | NA | 3 of 5 studies observed an increase in adherence, but only 1 study reported a significant difference between intervention vs. control. The 2 studies that did not observe differences between groups cite methodological concerns  2 of 5 studies observed a decrease in viral load  1 of 4 studies observed a significant increase in CD4 count at 3 months post baseline not sustained at 6 months | Intervention studies in females  High quality studies with larger populations  Humanistic (quality of life and patient satisfaction) and economic outcomes  Adequately trained professionals developing motivational interviewing skills  Universally accepted measure of adherence that includes how medication was taken (swallowed, crushed, with or without food) and when medication taken (before bed, appropriate time intervals) |
| [Robbins et al. (2014)](https://www.ncbi.nlm.nih.gov/pubmed/?term=Optimizing+ART+Adherence%3A+Update+for+HIV+Treatment)  US and Non-US | Qualitative synthesis | PWH | RCT and non-RCT  2013-2014  K=10  N=NR | 6  (medium) | Adherence: self-report, pill count,  pharmacy refill,  MEMS  Biologic:  viral load,  CD4+ count,  HIV RNA | Behavioral interventions | NA | Results were mixed due to the many small scale studies included  5 of 6 counseling based interventions were effective at improving medication adherence.  Computer-based technology was helpful to lay counselors offering better adherence counseling than standard.  2 of 3 cell phone based interventions each observed improvements in adherence outcomes | Long-term studies that follow participants over time.  Research on the barriers to adherence such as mental health and substance abuse  Structural level interventions; Provider-patient level interventions |
| [Simoni et al. (2006)](https://www.ncbi.nlm.nih.gov/pubmed/?term=efficacy+of+interventions+in+improving+highly+active+antiretroviral+therapy+adherence+and+hiv-1+rna)  US and Non-US | Quantitative Synthesis (Meta-analysis) | PWH | RCT  1996-2005  K=19  N= NR | 10  (high) | Adherence:  self-report,  electronic monitoring\_  Biologic:  viral load | Behavioral Intervention-cue dosing  -cognitive behavioral therapy  -external reminders (pagers) | Effects higher for intervention arm compared with controls:  Self-report adherence:  OR = 1.50 (95% CI: 1.16 to 1.94)  Viral load:  OR = 1.25 (95%CI: 0.99 to 1.59) for | Wide variety of intervention strategies were efficacious.  Intervention effects are larger when using subjective measures of adherence  Stratification analysis revealed a stronger intervention effect with studies using a longer recall period (2wks/1mo) vs. a shorter one (≤7 days) (*QB* = 3.97; P < 0.05) | Interventions addressing characteristics of the provider, medication regimen, and macro-level factors such as clinic accessibility  Application in resource-constrained settings and clinical settings |
| Directly Observed Therapy | | | | | | | | | |
| [Ford et al. (2009)](https://www.ncbi.nlm.nih.gov/pubmed/19954833)  US and non-US | Quantitative Synthesis (Meta-analysis) | Adult PWH | RCT  Thru 2009  K=12  N=1,862 | 10  (high) | Adherence: self-reported adherence  Biologic:  viral suppression, immunologic progression (CD4+ cell count), resistance mutations, new or recurrent AIDS-defining illness | DAART intervention | Overall intervention effect estimate was not significant for: viral suppression (RR: 1.04, 95% CI; 0.91-1.20, p=0.55),  self-reported adherence (pills missed) (RR: 1.02, 95% CI: 0.98-1.06, p=0.29),  CD4+ count (weighted mean diff: 0.35, 95% CI: 2.49-3.20, p=0.80)  Subgroup analysis: DAART improved viral suppression in drug users and homeless populations (RR: 1.31, 95% CI: 1.00-1.71, p=0.0464) but not general populations (RR: 0.96, 95% CI: 0-75.9, p=0.24)  No difference observed for full versus partial DAART, country of origin, study duration | DAART did not improve medication adherence when compared with self-administered antiretroviral treatment. | Targeted interventions with finite duration and specific populations |
| [Hart et al. (2010)](https://www.ncbi.nlm.nih.gov/pubmed/20375848)  US and non-US | Quantitative Synthesis (Meta-analysis) | Adult PWH | RCT and non-RCT  1995 – 2009  K=17  N=NR | 10  (high) | Adherence: proportion ≥ 95% adherence to prescribed dose  Biologic: undectable viral load, immunologic response, | DAART intervention | Effective in participants achieving undetectable viral load (RR:1.24, 95% CI: 1.08, 1.41), CD4 cell count (WMD:43, 95% CI: 12-74), and proportion achieving ≥95% adherence (RR:1.17, 95% CI: 1.03 – 1.32) | Intervention effectiveness was not significant on virologic suppression when study design restricted to RCTs.  Subgroup Analysis:  DAART effective among treatment experienced populations and substance abusers.  Non-clinic based DAART and additional adherence support increases the effectiveness of DAART programs. | Long-term benefits of DAART support  Cost-effectiveness analysis  Large scale DAART-HAART programs |
| Medication Dosing Regimens | | | | | | | | | |
| [Nachega et al. (2013)](https://www.ncbi.nlm.nih.gov/pubmed/24457345)  NR | Quantitative synthesis (meta-analysis) | PWH | RCT  Thru March 2013  K=19  N= 6312 | 10  (high) | Adherence: pill count,  MEMS  Biologic:  viral suppression | Once-daily vs twice-daily regimens in either ART naïve or -experienced patients | Negative significant assoc. for twice daily regimen : (Spearman correlation = −0.67; 95% CI, −.86 to −.37;  P = .001) but not the once daily regimen (Spearman correlation  = −0.22; 95% CI, −.60 to .25; P = .35).  Sig negative association observed between pill burden and virological suppression for both regimens (Spearman correlation  = −0.70; 95% CI, −.84 to −.49; P < .0001),  Adherence declined significantly over time | Once daily  ART regimens increased adherence when compared  with twice-daily regimens, but the difference was modest and  not associated with a difference in virological suppression  .Higher pill burden assoc with lower virological suppression  Higher Pill burden was associated with lower adherence.  Aherence was  higher with once-daily ART regimens than with twice-daily regimens  when adherence was measured objectively using pill counts and/or MEMS caps.  Once-daily dosing was  only statistically significant in treatment-naive persons and  in those who switched from twice- to once-daily dosing with virological  failure. | Research that investigates the impact of switching regimens on virologic outcomes (e.g., from single-tablet regimens to once-daily multi-tablet) |
| Patient Support and Education Interventions | | | | | | | | | |
| [Kenya et al. (2011)](https://www.ncbi.nlm.nih.gov/pubmed/21518221)  US | Qualitative Synthesis | PWH | RCT and non-RCT  Thru 2010  K=16  N=NR | 5  (medium) | Biologic:  CD4+ cell count, viral load | Community health workers | NA | CHW interventions are a cost-effective MA intervention that does not require physician to implement**.**  13 of 16 studies reported CHW was effective at improving HIV viral load and/or CD4 cell count.  Peer education and DAART most effective | What CHW strategies most effective?  CHW interventions needed in USA and in various subpopulations (e.g., age, ethnicity) |
| [Rueda et al. (2006)](https://www.ncbi.nlm.nih.gov/pubmed/16855968)  US and Non-US | Qualitative synthesis | PWH | RCT  1996 - 2005  N=19  K=2,159 | 10  (high) | Adherence: electronic monitoring, pill counts, medication diaries, patient self-report, provider report, clinic and pharmacy records  Biologic:  NR | -patient education,  -counseling and support -health promotion  -reminders provision of resources  -supervision -consulting  -telephone hotlines | NA | Adherence results were mixed.  Interventions implemented at the individual level vs group, long-term (>12 wks), targeted medication management skills (e.g., memory aids, text messaging) vs. cognitive behavioral approaches were most effective  Biologic results were mixed. Studies that reported significant findings also observed non-significant results for a different virologic outcome or timepoint  Interventions targeting marginalized populations (e.g., women, Latinos) were not effective | Most studies were pilot studies so more large studies needed.  Standardized adherence trials  Evidence revealing improvements in adherence translate to improved biologic outcomes  Evidence that targeted interventions are effective (e.g., women, latino) |
| Pharmaceutical Interventions | | | | | | | | | |
| [Rocha et al. (2015)](https://www.ncbi.nlm.nih.gov/pubmed/25810127)  US and Non-US | Quantitative (meta-analysis) | PWH | RCT  Thru July 2013  K=4  N=319 | 9  (high) | Adherence:  NR  Biologic:  CD4+ count,  immune failure,  viral load,  virologic failure,  virologic suppression,  viral resistance | Pharmacist provided care | Adherence (OR: 1.47, 95% CI: 0.81-2.65) (k=4) and virologic suppression (OR: 1.95, 95% CI: 0.61-6.25) (k=3) improved but not significantly  Sensitivity analysis: Only assessing studies implemented by pharmacists, assessing only MEMS data, and removal of study with the greatest weight did not result in significant findings. | Pharmaceutical interventions might improve ART adherence and virologic suppression, although differences between groups were not statistically significant. | RCT with larger samples to assess pharmaceutical interventions to improve ART |
| [Saberi et al. (2012)](https://www.ncbi.nlm.nih.gov/pubmed/22536064)  US & Non-US | Qualitative synthesis | PWH | RCT, non-RCT, cohort, Before/After Comparison, Ecological, Historically Controlled  1980-2011  K=32  N=NR | 9  (high) | Adherence:  NR  Biologic:  CD4+ count, viral load | HIV Clinical Pharmacistsengaged | NA | Adherence was 2%-59% higher in the pharmacist arm compared with control arm (k=9).  In 4 additional studies, ART adherence was improved in the pharmacist intervention compared with no pharmacist contact.  6 of 9 studies measuring viral load observed statistically significant improvements.  Studies that measured CD4 count observed some improvements (2 of 7 studies) when pharmacists played a central role. | Mixed methods research , including qualitative and quantitative studies  Cost-effectiveness studies  Expansion of pharmacist responsibilities beyond the “traditional” functions (e.g., assessment of ARV accuracy) |
| Miscellaneous HAART Adherence Improving Interventions | | | | | | | | | |
| [Bärnighausen, et al. (2011)](https://www.ncbi.nlm.nih.gov/pubmed/22030332)  Non US  (Sub-Saharan Africa) | Qualitative | PWH | RCT and non-RCT  2003-2010  K=26  N=NR | 11  (high) | Adherence:  NR  Virologic/  Immunologic:  Not specified | Any ART adherence improving interventions | NA | Results were inconsistent across outcomes and time.  16 of 26 studies revealed greater improvements in adherence for the intervention group vs. comparison group.  Interventions that observed significant intervention effects:  structured teaching programs, food rations, DAART, treatment supporters with and without DAART, non-physician providers, different models of ART delivery, and mobile-phone text messages  10 of 15 RCTs,  6 of 7 cohort studies, and 3 of 5 before-and-after studies revealed  improved adherence, according to at least one outcome  measure | Long-term follow-up (>1 year)  More Controlled trials needed to test effectiveness while accounting for confounders  Economic studies |
| [Bonner et al. (2013)](https://www.ncbi.nlm.nih.gov/pubmed/23774877)  US and Non-US | Quantitative  (Meta-analysis) | Viremic patients living with HIV  (detectable viral load) | Non-RCT  Thru 2012  K=8  N=NR | 8  (high) | Biologic:  viral load, viremic resupression (decrease in viral load following a previous elevated viral load despite ART) | Any ART adherence improving interventions that included viral load monitoring to reinforce adherence | Five  studies reported on proportion of patients with viremic resuppression Pooled estimate:  70.5% (95% confidence interval: 56.6% to 84.4%).  The remaining 3 studies all reported declines in mean viral load. | In patients with a detectable viral load, viral load monitoring can result in a reduction in viral load levels.  This might allow patients to stay on more affordable, less  complex, first-line regimens. | Interventions implemented in low-income countries  Operational research  Simpler automated devices for viral load testing |
| [Chaiyachati et al. (2014)](https://www.ncbi.nlm.nih.gov/pubmed/24849479)  US and non-US | Qualitative synthesis | PWH | RCT and non-RCT  2010-2012  K=124  N=NR | 10  (high) | Adherence: self-report  pill-count  pharmacy refill  electronic monitoring  Biologic:  viral load,  CD4+ cell count | Any ART adherence improving interventions | NA | Most intervention studies were effective at improving any 1 outcome. CBT, education, treatment supports, DAART and active reminders observed strong evidence of effectiveness.  Ongoing evaluation needed since intervention effectiveness was observed in some settings but not other settings  Less than 50% of intervention studies found positive results for both any 1 biological and 1 subjective/objective measure.  Counseling interventions (63%) followed by nutrition support (43%), DAART (30%), and drug treatment (40%) had the highest percentage of positive effects for both biological and subjective/objective outcomes.  Persons who use drugs were the most commonly researched and 12 of 22 studies observed significant intervention effects. | Limited evidence available on alternative health system structures for ART delivery, nutrition support, financial incentives, passive reminder devices, drug use treatment, and anti-depressive treatment  Cost-effectiveness analysis  Information on what components of multi-component interventions are effective  Interventions that examine sustained intervention effects  Technological enhancements in measuring adherence |
| [Charania et al. (2014)](https://www.ncbi.nlm.nih.gov/pubmed/24043269)  US only | Qualitative synthesis | PWH | RCT and non-RCT  1996-2011  K=9 studies, 10 interventions  N=NR | 9  (high) | Adherence: electronic monitoring, MEMS, pill count, self report, or pharmacy refill  Biologic:  viral load | Any ART adherence improving interventions | NA | 10 evidence based interventions observed improvements in medication adherence.  Only 1 of 10 intervention studies reported significant effects on both viral load and adherence behavior.  3 studies reported sig increases in adherence only and 3 studies reported sig increases in viral load only.  10 studies were considered “good” evidence based interventions but failed to meet “best” quality.  Studies that did not meet EBI criteria were due to small sample size, low retention rates, null findings. | Scalable and cost-effective interventions  Gold standards for adherence measurement in research and practice |
| [Fogarty et al. (2002)](https://www.ncbi.nlm.nih.gov/pubmed/?term=patient+adherence+to+hiv+medication+regimens+a+review+of+published+and+abstract+reports)  US and Non-US | Qualitative synthesis | PWH | RCT and non-RCT  Thru 1999  K=16  (11 reported intervention outcome data)  N=NR | 6  (medium) | Adherence: self report or medical chart review  Biologic:  undetectable viral load, CD4+ count, plasma assay, lab reports | Any ART adherence improving interventions | NA | 4 of 5 RCTs found no difference between intervention and control groups.  DAART (1 study) was effective immediately post-intervention  3 of 5 RCTs did not provide usual care, but instead a weaker adherence-improving interventions  4 of 6 non-RCTs (no control group) reported intervention effects over time; only half reported statistical significance for findings | Larger studies with more statistical power  Interventions that examine sustained intervention effects |
| [Mathes et al. (2013)](https://www.ncbi.nlm.nih.gov/pubmed/?term=Adherence-enhancing+interventions+for+highly+active+antiretroviral+therapy+in+HIV-infected+patients+-+A+systematic+review)  US and non-US | Qualitative synthesis | Adult PWH | RCT or cluster RCT  2001-2012  K=21  N=NR | 10 (high) | Adherence:  NR  Biologic: CD4+ cell count, viral load | Any ART adherence improving interventions | NA | Motivational interviewing vs. education revealed significant effects on adherence rate and viral load in 1 study.  Strengthening family support vs. psychoeducation  for drug-dependent women had a statistically  significant effect on the viral load and CD4 cell count,  but not adherence rate in 1 study.  Across studies, no strategy was consistently effective. | Intervention sustainability  Long-term benefits (e.g., AIDS or mortality) |
| [Mathes et al. (2014)](https://www.ncbi.nlm.nih.gov/pubmed/24966025)  Non-US  (sub-Saharan Africa) | Quantitative synthesis | Adult PWH | RCT  1995-2013  K=6  N=NR | 9  (High) | Adherence:  NR  Biologic: CD4+ count, viral load | Any ART adherence improving interventions | Risk of nonadherence lower in patients receiving text messaging interventions (RD: -0.10, 95% CI: -0.17, -0.03) (k=2)  DAART interventions compared with controls did not improve viral load (RR: 1.03, 95% CI: 0.78-1.36) (k=3) | Adherence enhancing interventions were in the direction of improving adherence outcomes but not viral load. | Standardized measure of adherence across studies  High quality RCT tailored to specific settings and in nonadherent patients  Studies with longer follow-up that asses patient or clinical outcomes |
| [Mbuagbaw et al. (2015)](https://www.ncbi.nlm.nih.gov/pubmed/25825938)  US and non-US | Qualitative Synthesis | PWH | RCT  1999 to 2013  K=49  N=NR | 8  (high) | Must include both adherence and clinical outcomes  Adherence:  NR  Biologic:  viral load, T-lymphocyte cell count, | Any ART adherence improving interventions | NA | 27 studies improved at least one adherence outcome.  16 studies improved at least one clinical outcome  6 studies improved clinical outcomes with no improvements in adherence  10 studies improved both adherence and clinical outcomes  26% of patient-related adherence interventions improved both outcomes  15% and 36% of high income and low income studies, respectively, improved both outcomes  17% that used a theoretical framework improved both outcomes  20% of technology based interventions improved both outcomes Few interventions improved both adherence and clinical outcomes.  No clear factors identified that explained intervention effectiveness  Benefits of theoretical frameworks in adherence research remains unclear and improving adherence might require more than one single theory. | High quality adherence interventions in younger populations and high disease burden settings  Gold standard adherence outcome assessment tool  Cost-effectiveness studies |
| [Mills et al. (2014)](https://www.ncbi.nlm.nih.gov/pubmed/?term=Interventions+to+promote+adherence+to+antiretroviral+therapy+in+Africa%3A+a+network+meta-analysis)  Non-US (Africa) | Quantitative Synthesis  (network meta-analysis) | PWH | RCT  Thru 2014  K=14  N=7110 | 6  (medium) | Adherence: proportion meeting trial defined criteria  Biologic:  viral suppression | Any ART adherence improving interventions | Interventions effective at improving adherence were:  Enhanced Standard of Care (SOC: OR: 1.46, 95% credibility interval [CrI] 1.06–1.98)  Weekly text messaging  messages vs SOC (1·65, 1·25–2·18) and daily text messaging (1.56 (1.01–2.40)  Enhanced SOC plus weekly text messages vs. SOC (1.65, 1.25-2.18) and alarm (2.06, 1.03-4.11)  Counselling and plus text messaging (2.07, 1.22–3·53)  Treatment supporters (1.83,  1.36–2.45)  Interventions effective at improving viral suppression were:  Weekly text messages (1.55, 1.01–2.38)  Enhanced SOC plus treatment supporter (1.46, 1.09-1.97)  Calendars, alarms, and basic SOC were did not statistically significantly improve outcomes | Enhanced SOC improved adherence outcomes  Adherence further improved when combined with weekly SMS messages and treatment supporters.  Insufficient evidence to support alarms, daily SMS messages and calendars  Weekly but not daily SMS messages were effective at improving outcomes | Lack of evidence in specific populations such as HIV-infected children, adolescents, pregnant women, prisoners, and MSM |
| [Simoni et al. (2003)](https://www.ncbi.nlm.nih.gov/pubmed/14724327)  US and Non-US | Qualitative synthesis | PWH | RCT and Non-RCT  Thru 2003  K=21  N=NR | 8  (high) | Adherence:  NR  Biologic:  NR | Cognitive and behavioral, behavioral only, modified DAART | NA | Two studies observed improvements in self-report adherence  10 studies observed improvement in virologic or immunologic outcomes.  Few studies tested for statistical significance and most lacked a control condition. | Combined interventions because single component interventions observe smaller effects  Provider based interventions  Cost effectiveness data  Accurate and well accepted measure of adherence  Clear approach to addressing barriers |
| [Yang et al. (2014)](https://www.ncbi.nlm.nih.gov/pubmed/?term=State+of+the+science%3A+The+efficacy+of+a+multicomponent+intervention+for+ART+adherence+among+people+living+with+HIV.)  US and Non-US | Qualitative synthesis | Adult PWH | RCT  1997-2008  K=11  N=NR | 5  (medium) | Adherence: pill count, self-report  Biologic:  CD4 count,  RNA viral load | Multi-component adherence enhancing intervention (must include an individual education session and 1-3 complementary aids) | NA | 7 studies observed significant improvements in adherence outcomes. Remaining studies observed statistically non-significant improvements in adherence outcomes.  Interventions targeting individual’s medication management skills were successful  Combining strategies of individualized education, adherence tools, and addressing barriers were also effective at improving adherence  3 of 9 studies improved viral load but no studies were revealed an improvement in CD4 count | Cost-effectiveness studies  Valid, reliable, and objective methods of measuring adherence |
| Children and Young People Living with HIV/AIDS | | | | | | | | | |
| [Arrivillaga et al. (2013)](http://www.tandfonline.com/doi/figure/10.1080/17450128.2013.764031?scroll=top&needAccess=true)  US and Non-US | Qualitative Synthesis | Patients aged 24 and under | RCT and Non-RCT  2000-2012  K=16  N=NR | 6  (medium) | Adherence:  child or caregiver report, pill count, pharmacy records, medical records  Biologic:  Virologic and  immunologic  response, viral load, CD4 count | Pediatric or adolescent medication adherence interventions  -Adherence only  -Comprehen  ive interventions | NA | 6 studies examined adherence only interventions. Medical interventions (GI-tube insertion, dosing regimen) observed improvements in adherence and viral load. Behavioral interventions  10 studies examined comprehensive interventions and 6 provided effectiveness data. 5 of 6 intervention studies observed improvements in adherence or biologic outcomes.  Comprehensive interventions compared with control conditions more effective at dealing with complexities of MA in children | Interventions conducted in Africa, Asia, Latin America, or the Caribbean  More comprehensive interventions needed in children/adolescents/majority were pilot studies |
| [Bain-Brickley et al. (2011)](https://www.ncbi.nlm.nih.gov/pubmed/22161452)  US and Non-US | Qualitative Synthesis | Children and adolescent (age ≤ 18 years) | RCT and non-RCT  1980-2010  K=4  N=NR | 10  (high) | Adherence: child or caregiver report, pill count, volume measurement, unannounced home visit/pill count or electronic monitoring  Biologic:  Clinical or virologic failure;  Viral load,  CD4 counts, | Home-based nursing  -Medication diaries  -Peer support group therapy  -Dosing regimens | NA | RCT studies (n=2) observed improvements in self-and caregiver-report adherence, viral load, and CD4 count compared with controls but the difference was not statistically significant.  A statistically significant improvement in pharmacy refill was observed in one study, however no difference was observed in self-reported adherence.  One Non-RCT study observed non-significant improvements in viral load and no difference in CD4 cell counts compared with controls.  One non-RCT regimen based study observed higher rates of virological suppression in PI-based regimens compared with NNRTI-based regimen (p=0.02) | Consistent measures of adherence  RCT with larger sample sizes |
| [Reisner et al. (2009)](https://www.ncbi.nlm.nih.gov/pubmed/19270345)  US | Qualitative Synthesis | Youth (ages 13 to 24 years) | RCT and non-RCT  1999-2008  K=7  N=NR | 6  (medium) | Adherence: Self-report, Pharmacologic measures (pill count, pharmacy refill records, electronic monitors)  Biologic: plasma HIV RNA, CD4+count, plasma assay, laboratory reports | -DAART  -Dosing changes  -Text-message reminders  -Education and counseling | NA | Hospital-based DAART intervention studies (k=3) observed improvements in plasma HIV RNA levels while under direct supervision, however HIV RNA levels increased as time after discharge increased  Regimen-related intervention studies (k=2)(once-daily dosing and text message reminders) improved viral loads and CD4+ count outcomes  Education and counseling interventions (k=2) observed only ~50% of participants in one study self-reported medication adherence most or all of the time. Whereas a second study saw improved CD4+ counts. | Larger, rigorous studies are needed  Few studies examined specific subgroups (e.g., gay and lesbian youth, racial or ethnic minority youth)  Culturally-tailored interventions that focus on specific populations of youth (e.g., homeless, sexual minorities)  Cost-effectiveness data |
| [Shaw & Amico 2016](https://www.ncbi.nlm.nih.gov/pubmed/26959190)  US & Non-US | Qualitative Synthesis | Youth and young adults 13-24 years of age | RCT and Non-RCT  Thru 2015  K = 10  Sample size range= 4-108 | 8  (high) | Adherence:  Self-report, MEMS Caps, pill count  Biologic:  Viral load, CD4 count | -Multi-systematic therapy  - Motiv. Interviewing  -CBT  -text messaging  -education  -DOT  -Financial incentives  -family system therapy | NA | 2 of 3 Level 1 studies with RCT design and significance testing observed improvements in adherence and biologic outcomes.  1 Level 2 study with within group design and significance testing observed improvements in adherence and viral load.  1 Level 3 study with a RCT design and descriptive outcomes observed improvements on adherence only.  3 of 5 Level 4 studies with a within-group design and descriptive outcomes observed improvements in adherence. All studies improved viral load. | Few studies targeted key populations  Small sample size of included studies with low power  More non-US studies |
| [Simoni et al. 2007](https://www.ncbi.nlm.nih.gov/pubmed/17533177)  US | Qualitative Synthesis | Youth and young adults 3-24 years of age | NR  1999-2005  K=7  Sample size range= 10-262 | 5  (medium) | Adherence: Self-report, caregiver report, medical chart review, clinic attendance, pill count, pharmacy refill, electronic drug monitoring, DAART, resistance testing  Biologic:  Viral load, CD4 count, biological assay of drug in bodily fluid | Pediatric adherence intervention  -DAART  -GI Tube  Insertion  -education and counseling  -home nurse | NA | A 12-week educational program improved adherence 3 months after intervention  DAART and multi-systemic family therapy improved viral load.  GI tube insertion improved both adherence and/ viral load.  Home nursing visits and a 18 week intensive adherence program observed marginal improvements in adherence.  1-time interventions in the absence of ongoing education and support might be insufficient. | Long-term prospective studies  Interventions that address normative developmental tasks experienced by children (e.g., achieving mastery)  Interventions that emphasize self-efficacy and social problem-solving |
| Persons who Use Drugs | | | | | | | | | |
| [Binford et al. 2012](https://www.ncbi.nlm.nih.gov/pubmed/?term=binford+hiv+drugs+intervention)  US & Non-US | Quantitative Synthesis | PWH and who use drugs or alcohol | RCT; Cohort; Prospective  1997-2011  45  N=NR | 10  (high) | Adherence: pill counts  -electronic pill bottle caps (MEMS)  -self-reported recall  -pharmacy refill data  Biologic:  viral load and CD4 cell count | Adherence-based interventions in current and/or past adult drug users | NA | Directly administered antiretroviral therapy (DAART) alone or in combination with medication-assisted therapy (MAT) programs revealed consistently significant improvements in adherence, viral load, and increased CD4 counts at short-term follow-ups.  Less consistent data to support other interventions  Short-term improvement of outcomes in nurse-delivered multi-component and contingency management interventions.  Interventions including DAART did not demonstrate long-term treatment outcomes post-intervention. | Long-term follow-up evaluations  ART adherence interventions with booster sessions  Interventions in ART-naïve PWUDs |
| Persons with Co-Occurring Mental Illness | | | | | | | | | |
| [Palmer et al. (2010)](https://www.futuremedicine.com/doi/10.2217/hiv.10.4)  US and Canada | Qualitative Studies | PWH  and co-occurring mental illness | RCT and Non-RCT  Thru 2006  N=4  N=NR | 5  (medium) | Adherence: MEMS,  self-report  Biologic:  viral load | Adherence-based intervention focused on persons with mental illness | NA | Two RCTs reported improvements in medication adherence, as well as in depression resulting from the intervention  Of the 3 studies that assessed adherence, results were mixed. 1 of the 2 studies in psychiatric patients observed improvements in adherence (MEMS) up to 12 months post-intervention.  1 study reported no improvements in adherence or viral load; but greater intervention exposure was associated with improved self-report adherence. | Explanatory models of adherence and nonadherence that account for psychiatric illnesses.  Research on the impact of serious and persistent mental illness and medication adherence. |