Interventions to Enhance Adherence to IFN-free HCV Therapy Among People Who Inject Drugs

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Evidence-based interventions to enhance adherence in the chronic Hepatitis C care continuum

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Review

Evidence-based interventions to enhance assessment, treatment, and adherence in the chronic Hepatitis C care continuum

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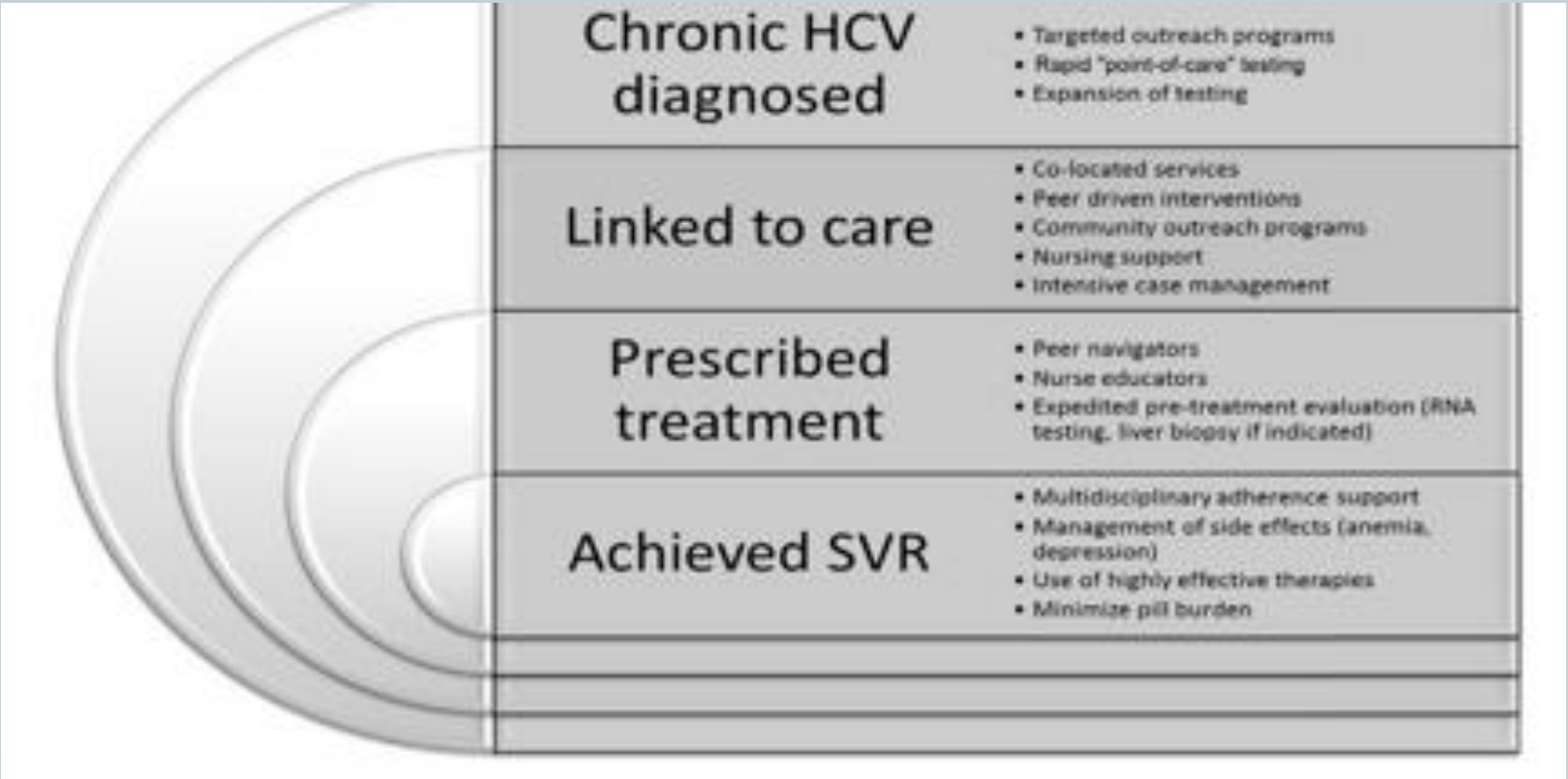
Hepatitis C Care Continuum



Background

- High levels of adherence to IFN-based regimens correlate with early virologic response (EVR) and SVR. (Lo Re et al; McHutchison et al)
- It's unclear what level of adherence is optimal to achieve SVR with non-interferon-based regimens that are more potent and durable, but with potentially lower barriers to developing genotypic resistance
  - Developed for statistical analyses in IFN-era cohort studies, the 80/80 rule defines optimal adherence as having taken at least 80% of prescribed doses at least 80% of the time
- It's unknown whether adherence to DAAs is problematic enough to warrant targeted intervention given lower pill burdens and shorter treatment courses.

Methods

- Systematic review of published scientific literature using IOM guidelines: PubMed, Medline, Google Scholar, EmBASE, and PsychInfo
  - Key words: “Hepatitis C”, “surveillance,” “testing,” “adherence,” “treatment,” and “intervention”
  - Additional references from citation indices
- Titles and abstracts were screened by 3 independent authors for following inclusion criteria:
  - In English, full text available, original research, described intervention with measurable outcomes, and published between 2001 and 2014.
- Full texts of abstracts were further reviewed and critical data extracted for analysis.
- Final studies selected through an iterative process with 3 authors (inclusion criteria applied to manuscripts which were categorized by topic area)

Four Topic Areas

- Diagnosis and case-finding
- Linkage to care
- Pre-therapeutic evaluation and treatment initiation
- **Treatment adherence facilitation**

Results of Systematic Review

- 33 published studies relating to HCV treatment adherence interventions
  - 16 were excluded because they did not describe a specific intervention.
- Adherence defined in various ways
  - 80/80 adherence rule (Alam et al; Carrion et al, 2013)
  - Attendance at study visits (Ho et al, 2013)
  - Treatment completion - treatment persistence vs. adherence (Bertino et al, 2010; Bonkovsky et al, 2008)
- Adherence measured in various ways
  - Pill counts (Litwin et al, 2011)
  - Pharmacy claims (Ho et al, 2013; Hussein et al; 2010)
  - MEMS (Bruce et al, 2012)

Methadone Clinics

Author, Year Sample Size Setting	Intervention	Study Design	Major Findings
Bonkovsky, 2008 48 MMT patients Methadone Clinics	Peginterferon alfa-2a DOT vs. SAT (self-administered treatment)	Prospective Multicenter Randomized trial	No significant difference in treatment completion between DOT and SAT
Bruce, 2012 21 MMT patients Methadone Clinic Hepatology Clinic	mDOT (AM RBV with methadone + weekly IFN) vs. SAT	Pilot RCT	Fully integrated HCV and MMT care is feasible but logistically challenging
Litwin, 2011 40 MMT patients Methadone Clinic	Enhanced DOT (RBV + IFN) versus Standard DOT (IFN only)	RCT	DOT feasible **Preliminary results: 88% adherence to RBV in enhanced DOT vs. 77% standard DOT, p=0.02)** No difference in SVR

Drug Treatment Centers

Author, Year Sample Size Setting	Intervention	Study Design	Major Findings
Curcio, 2011 16 toxicologically stable vs. 32 matched controls Drug Addiction Center in Naples, Italy	Multidisciplinary Support Program (MSP) "Together to take Care"	Case control (matched 2:1)	**Adherence: 75% MSP vs. 41% TAU** **Abstinence: 63% MSP vs. 22% TAU** **SVR: 69% MSP vs. 46% TAU**
Waizmann, 2010 49 HCV enrolled in OAT Outpatient drug treatment program, Germany	PEG-IFN + once-daily RBV	Retrospective open-label cohort study	**48 / 49 (98%) achieved SVR**

Hepatology / Liver Units

Author, Year Sample Size Setting	Intervention	Study Design	Major Findings
Carrion, 2013 447 HCV: IFN/RBV Liver Unit in Spain	Multidisciplinary Support Program (MSP)	Non-randomized Controlled study	**Adherence and SVR higher in MSP compared to controls (G1/4 SVR: 68% vs. 49%, p=0.02)**
Larrey, 2011 244 HCV: IFN/RBV Liver Unit in France	Standardized Nurse consultation: adherence and efficacy of therapy after each visit vs. TAU	Multicenter Open-label RCT	Adherence 74% vs. 63% control, p=0.06 - more benefit for those on 48 weeks **Increased SVR (multivariate model)**
Zucker, 2010 20 HCV: IFN/RBV 2 hepatology practices in Massachusetts	Home walking program vs. TAU	Pilot RCT	Minimal effect of intervention on treatment completion

Primary Care Clinics

Author, Year Sample Size Setting	Intervention	Study Design	Major Findings
Grebely, 2007 40 HCV 2 multidisciplinary health clinics in Vancouver	mDOT (IFN as DOT, RBV as SAT)	Observational cohort study	**Overall SVR 55%** **No difference in SVR depending on intercurrent drug use**
Ramsey, 2011 29 HCV patients: IFN/RBV Stably enrolled in MMT Urban hospital-based primary care clinic	8-session CBT vs. TAU	RCT	Intervention had no effect on depression-related antiviral treatment failure, adherence, or SVR

Other Settings

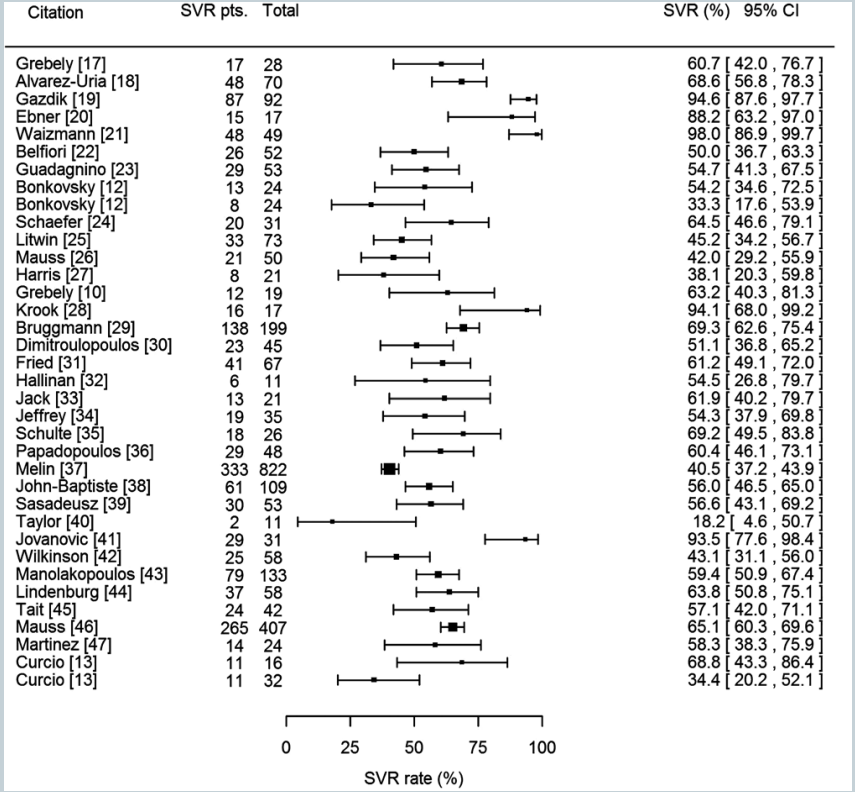
Author, Year Sample Size Setting	Intervention	Study Design	Major Findings
Ho, 2013 30 HCV Homeless Clinic	Multidisciplinary weekly group medical visit	Pilot study	**80% treatment adherence** **55% genotype 1** **80% genotypes 2/3** **(high prevalence homelessness, SUDs, serious mental illness)**
Morasco, 2010 39 HCV: IFN/RBV 2 VA Medical Centers	Prophylactic citalopram vs. placebo	Double-blind placebo controlled RCT	Intervention had no effect on IFN-induced depression, changes in depressive symptoms over time, or rates of treatment completion
Saiz de la Hoya 244 HCV: IFN/RBV Prison in Spain	DOT vs. SAT	RCT	High rates of treatment completion in both groups SVR 61% DOT vs. 66% SAT, $p>0.05$

Other Settings

Author, Year Sample Size Setting	Intervention	Study Design	Major Findings
Alam, 2010 503 HCV-monoinfected 33 U.S. sites	RibaPak (higher dose formulation of RBV vs. 200 mg tablets RBV)	Multicenter Observational Prospective Registry	**Those on RibaPak vs. 200 mg tablets significantly higher adherence**
Hussein, 2010 780 HCV patients: Peg IFN-alfa 2b/RBV enrolled in manufacturer-sponsored programs vs. 8572 controls Program Database	Be in Charge (BIC) patient support program	Retrospective cohort analysis by propensity score matching – BIC enrollees vs. matched controls not in BIC	**BIC subjects refilled significantly more injections vs. controls (6.7 more during 48 weeks) and were more likely to refill at least 12 injections in 12 weeks (72% vs. 64%, p<0.001)**
Reimer, 2013 189 HCV patients on stable OAT Germany	Manualized Weekly Psychoeducation (PE) group sessions vs. TAU	Non-randomized Controlled multicenter study	No significant effect of PE on retention **Effect of PE on SVR only when at least 5 PE sessions attended** (no effect in ITT analysis)

Determinants of HCV Treatment Completion and Efficacy in People Who Use Drugs Assessed by Meta-analysis (Dimova et al, CID 2012)

- Pooled SVR = 56% (n=36 studies)
- SVR affected by genotype 1/4 and proportion of HIV co-infected DU.
  - After adjustment, <u>SVR increased with presence of multidisciplinary team.</u>

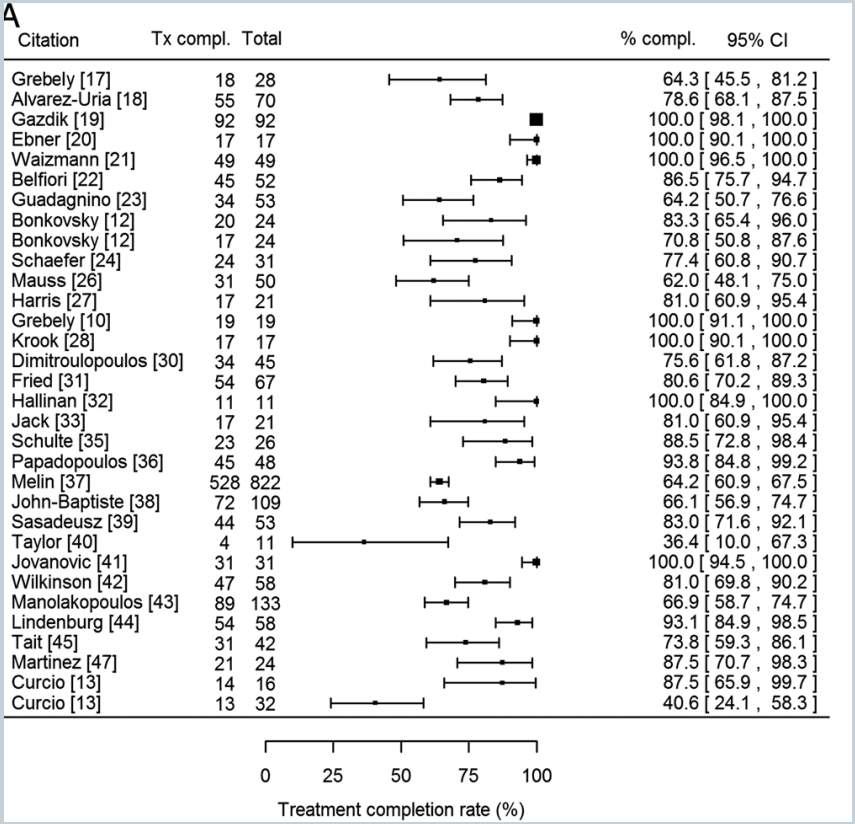


Determinants of HCV Treatment Completion and Efficacy in People Who Use Drugs Assessed by Meta-analysis (Dimova et al, CID 2012)

- Overall treatment completion = 83%

  (n=32 studies)

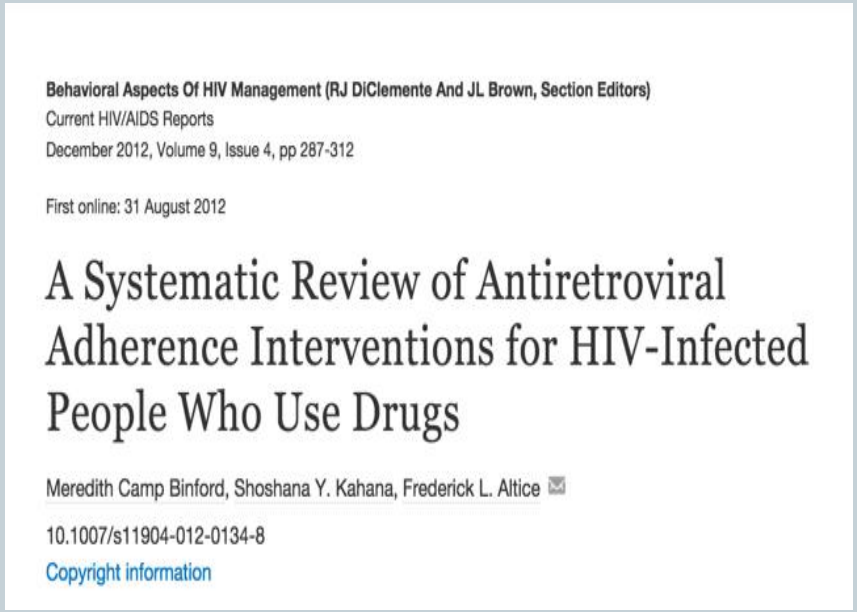
  - Addiction treatment increased HCV treatment completion.



Summary of Interventions from HCV Literature

- Lower pill burden (and potentially weekly blister packs) may be associated with improved adherence
- Although DOT in the IFN-era has been promising, it has not definitively better than treatment as usual
  - Treatment persistence may be more important than adherence in IFN-era making DOT less effective
  - studies in the DAA era are urgently needed
- Multidisciplinary programs seem to improve adherence and SVR
- No clear evidence for CBT or psychoeducation interventions

Systematic Review of Antiretroviral Adherence Interventions for HIV-Infected People Who Use Drugs



Behavioral Aspects Of HIV Management (RJ DiClemente And JL Brown, Section Editors)
Current HIV/AIDS Reports
December 2012, Volume 9, Issue 4, pp 287-312

First online: 31 August 2012

A Systematic Review of Antiretroviral Adherence Interventions for HIV-Infected People Who Use Drugs

Meredith Camp Binford, Shoshana Y. Kahana, Frederick L. Altice

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INVITED ARTICLE HIV/AIDS

Kenneth H. Mayer, Section Editor

Optimizing Care for HIV-Infected People Who Use Drugs: Evidence-Based Approaches to Overcoming Healthcare Disparities

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HIV Antiretroviral Adherence Interventions and Generalizability to HCV DAA Adherence Interventions

Intervention	Major Findings	Implications for HCV DAA-era
Medication-Assisted Therapy Interventions (Avants et al; Moatti et al; Springer et al; Palepu et al Roux et al)	MMT and BPN associated with increased adherence and virological success	Linking people who use drugs to MMT and BPN may increase adherence and SVR
Directly Administered Antiretroviral Therapy (DAART) or DOT (Altice et al; Macalino et al; Berg et al)	DAART improves adherence and virological suppression in mutiple settings (mobile van, MMT, community) Effects dissipate after DOT ends	DOT is likely to be associated with improved adherence and SVR especially with simple once-daily regimens where the majority of doses can be observed HCV treatment generally 12 – 24 weeks so DOT can occur throughout treatment

HIV Antiretroviral Adherence Interventions and Generalizability to HCV DAA Adherence Interventions

Intervention	Major Findings	Implications for HCV DAA-era
Contingency Management (CM) (Petry et al; Rigsby et al; Rosen et al)	-Short-term improvements in adherence; no persistence after vouchers completed -CM vs. 12 Steps groups showed greater reductions in HIV VL	Very promising for HCV with respect to both adherence and SVR as HCV treatment duration is short
Counseling Using Motivational Interviewing (MI) and/or Cognitive Behavioral Therapy (CBT) (Parsons et al; Parsons et	One RCT 143 HIV-infected alcohol drinkers (8-session MI/CBT): decrease in VL, increase in adherence and CD4 (not sustained)	Shows promise but may not be generalizable as difficult to implement MI/CBT sessions on a large-scale

HIV Antiretroviral Adherence Interventions and Generalizability to HCV DAA Adherence Interventions

Intervention	Major Findings	Implications for HCV DAA-era
Nurse-delivered Multi-component Interventions -Nurses trained in MI (multiple sessions and one home visit; alcohol; skills-building; self-efficacy and tailored) [Samet et al] -Nurse + community support worker (1 year home-visit intervention) [Williams et al] -Nurse home visits + telephone intervention (Wang et al)	Short-term improvements in adherence and viral suppression Improvement in adherence (>90%) Improvement in self-reported adherence (100%)	Promising strategies Could be implemented by nursing agencies which are already integrated within the community

HIV Antiretroviral Adherence Interventions and Generalizability to HCV DAA Adherence Interventions

Intervention	Major Findings	Implications for HCV DAA-era
Social Support and Peer-Driven Interventions (Broadhead et al; Deering et al; Purcell et al)	-Preliminary peer-driven interventions: improvements in short-term adherence -10-session peer mentoring intervention not associated with improved adherence	HCV studies needed Highly standardized peer interventions may not be as effective as less formal interventions
Educational Counseling (pilot study of HIV-infected African American people who inject drugs ; psychoeducation + weekly pill organizers)	Significant increase in adherence, medication refills, and appointments vs. baseline	HCV studies needed

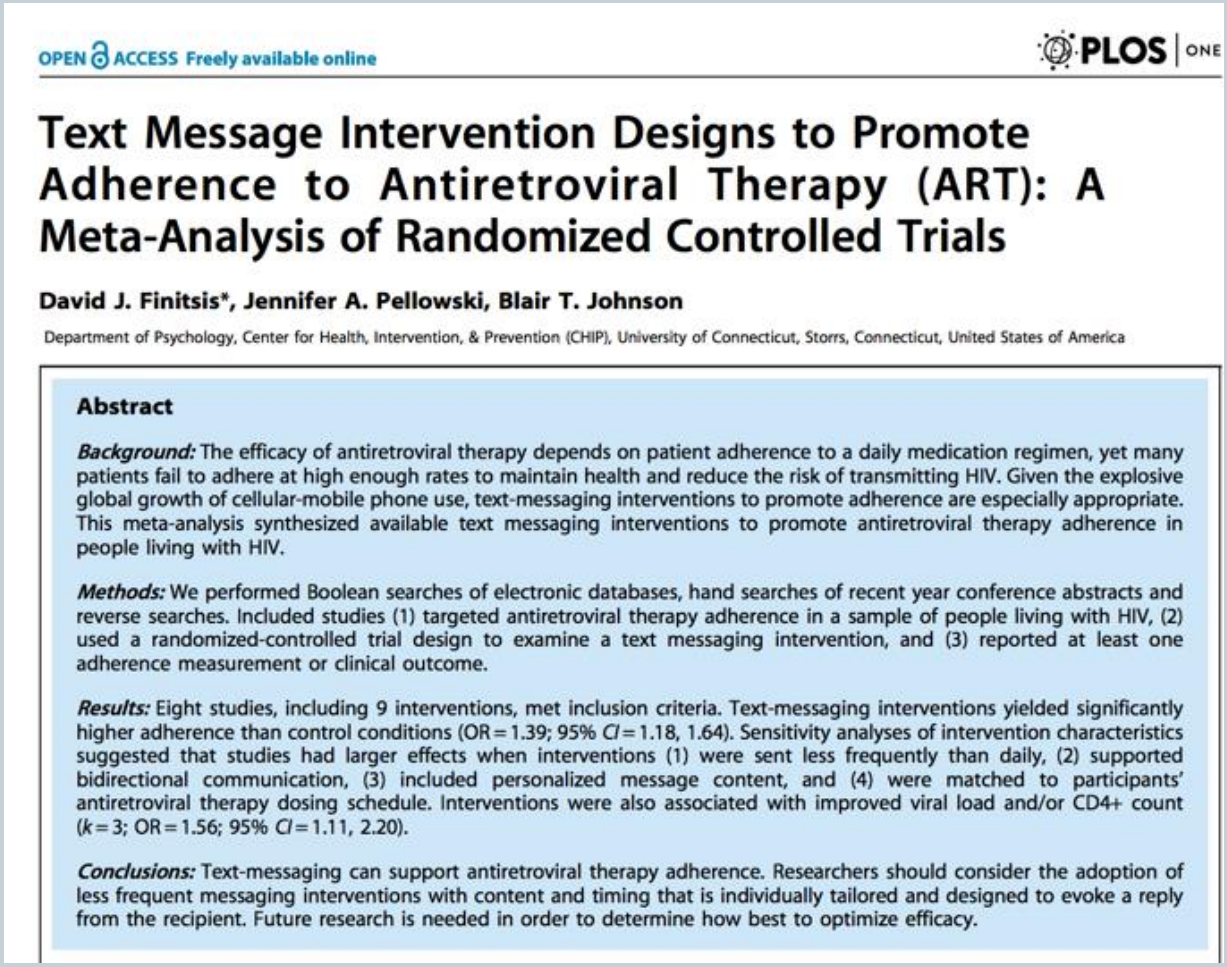
HIV Antiretroviral Adherence Interventions and Generalizability to HCV DAA Adherence Interventions

Intervention	Major Findings	Implications for HCV DAA-era
Adherence Case Management (Bamberger et al)	Limited data; Small study showed that 64% had viral suppression after 2 months	HCV studies needed
Time/Reminder Interventions* (Powell-Cope et al; Altice et al)	- One small study: did not improve adherence among HIV-infected PWID -Small pilot study for out of treatment PWID at mobile healthcare sites: 85% viral suppression at 6 months	HCV studies needed

HIV Antiretroviral Adherence Interventions and Generalizability to HCV DAA Adherence Interventions

Intervention	Major Findings	Implications for HCV DAA-era
Integrating Medication-Assisted Therapy with HIV Treatment -12 month RCT in which clinic-based treatment with buprenorphine and individual counseling vs. case management and referral to OAT program (Lucas et al) -Large observational cohort (Altice et al) -Small pilot studies integrating buprenorphine within HIV clinics (Cunningham et al; Sullivan et al)	-Those with integrated care with significantly more likely to receive substance abuse treatment, but no significant changes from baseline in adherence, VL and CD4. -Longer retention on buprenorphine treatment was significantly associated with retention and increased CD4 -Increase in adherence and CD4	Worth studying whether integrating buprenorphine within settings that serve as a medical home for people who inject drugs (e.g. primary care, HIV clinic, or harm reduction program) leads to improved HCV outcomes. May not be feasible in hepatology clinics or liver units.

Text Message Intervention Designs Promote Adherence to Antiretroviral Therapy



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Text Message Intervention Designs to Promote Adherence to Antiretroviral Therapy (ART): A Meta-Analysis of Randomized Controlled Trials

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Abstract

Background: The efficacy of antiretroviral therapy depends on patient adherence to a daily medication regimen, yet many patients fail to adhere at high enough rates to maintain health and reduce the risk of transmitting HIV. Given the explosive global growth of cellular-mobile phone use, text-messaging interventions to promote adherence are especially appropriate. This meta-analysis synthesized available text messaging interventions to promote antiretroviral therapy adherence in people living with HIV.

Methods: We performed Boolean searches of electronic databases, hand searches of recent year conference abstracts and reverse searches. Included studies (1) targeted antiretroviral therapy adherence in a sample of people living with HIV, (2) used a randomized-controlled trial design to examine a text messaging intervention, and (3) reported at least one adherence measurement or clinical outcome.

Results: Eight studies, including 9 interventions, met inclusion criteria. Text-messaging interventions yielded significantly higher adherence than control conditions (OR = 1.39; 95% *CI* = 1.18, 1.64). Sensitivity analyses of intervention characteristics suggested that studies had larger effects when interventions (1) were sent less frequently than daily, (2) supported bidirectional communication, (3) included personalized message content, and (4) were matched to participants' antiretroviral therapy dosing schedule. Interventions were also associated with improved viral load and/or CD4+ count ($k = 3$; OR = 1.56; 95% *CI* = 1.11, 2.20).

Conclusions: Text-messaging can support antiretroviral therapy adherence. Researchers should consider the adoption of less frequent messaging interventions with content and timing that is individually tailored and designed to evoke a reply from the recipient. Future research is needed in order to determine how best to optimize efficacy.

Promising HCV Interventions Based on HIV Interventions

- DOT in various settings (prison, primary care, mobile health settings, and methadone clinics)
- Medication Assisted Interventions (methadone and buprenorphine)
- Contingency Management
- Community-based nurse-led multicomponent interventions
- Text message interventions
- Small HCV pilot trials are needed: peer-driven, educational counseling, adherence case management, and other time/reminder interventions
- We can not eliminate any potential strategy at this stage!

Conclusions and Future Directions

- HCV studies described interventions with non-contemporary IFN-based treatments.
- Future research needs to address how these interventions apply (if at all) in the context of well-tolerated, simple, all-oral treatments
- Baseline adherence and SVR needs to be characterized to support the need for additional intensive interventions for people who inject drugs or for specific subgroups of people who inject drugs
  - Treatment settings are models of care are likely adherence interventions.
- We also need to characterize the relationship between adherence and SVR in the all-oral era. Real-world studies with less adherent patients are required.
- HIV-specific interventions might be modified to fit HCV and may be a better guide than IFN-era HCV studies.
  - Durability concerns with HIV NOT an issue with HCV
- Mobile technologies that target adherence may be a cost-effective method of reaching many PWID (e.g. texting interventions or smart phones with virtual DOT).
- Limitations: did not include 2015 HCV studies and some HIV studies (last 3 years) or studies in other languages. Additional studies may have been missed.

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