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BRIEF REPORT

Low Adherence Achieves High HCV Cure Rates Among People Who Inject Drugs Treated With Direct-Acting Antiviral Agents

Brianna L. Norton,[1] Matthew J. Akiyama,[1] Linda Agyemang,[1] Moonseong Heo,[2] Irene- Pericot-Valverde,[3] and Alain H. Litwin[3,4,5]

[1]Division of General Internal Medicine, Department of Medicine, Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, New York, USA, [2]Department of Public Health Sciences, Clemson University, Clemson, South Carolina, USA, [3]Clemson University School of Health Research, Clemson, South Carolina, USA [4]Department of Medicine, University of South Carolina School of Medicine – Greenville, Greenville, South Carolina, USA, and [5]Prisma Health, Greenville, South Carolina, USA

We measured hepatitis C virus (HCV) adherence via electronic blister packs for 145 people who inject drugs treated on-site in a methadone program. The overall sustained virologic response (SVR) rate was 96% (95% CI, 91%–98%), and overall daily adherence was 78% (95% CI, 76%–81%). Participants who achieved at least 50% adherence had an overall SVR rate of 99%, with each 5% adherence interval >50% achieving at least 90% adherence. Suboptimal adherence may still lead to cure in the direct-acting antiviral era.

Keywords. adherence rates; HCV; PWID.

People who inject drugs (PWID) constitute the majority of people with hepatitis C virus (HCV) in the United States [1]; however, access to direct-acting antivirals (DAAs) remains limited for PWID. The majority of PWID have not been treated, often due to concerns about poor adherence to treatment [2–4]. Though studies have shown high rates of sustained virologic response (SVR) for PWID in the DAA era [5, 6], adherence to the HCV treatment regimen has not often been rigorously measured. To help guide clinical decisions, it is crucial for providers to understand the degree of adherence necessary to achieve HCV cure in the era of DAAs, particularly for groups of patients who may have difficulties achieving perfect adherence, such as PWID.

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Correspondence: Alain Litwin, MD, MS, MPH, Department of Medicine, 701 Grove Road, 5th Floor Support Tower, Greenville, SC 29605 (alain.litwin@prismahealth.org).

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METHODS AND FINDINGS

The PREVAIL study was a 3-arm randomized controlled trial to assess the effectiveness of models of HCV care among 150 PWID on-site at opioid treatment programs [7]. All participants signed written informed consent, and the study was approved by the Einstein College of Medicine Institutional Review Board. HCV treatment was provided according to the American Association for the Study of Liver Diseases/Infectious Diseases Society of America (AASLD/IDSA) guidelines and delivered through directly observed therapy (DOT), group treatment (GT), or self-administered individual treatment (SIT). There were no stopping rules for participants with poor adherence. Here, we include 145 PREVAIL participants who were not deceased during treatment and had adherence data. Adherence was measured in all 3 arms using electronic Med-ic blister packs, which have a 99.6% event accuracy (time of dose removal correctly recorded within +2 minutes).

Blister pack protocols differed by study arm. For those participants randomized to GT, participants received interferon (for those receiving interferon-based therapy) and 7-day blister packs during each weekly group treatment session. Participants randomly assigned to SIT received office-based interferon, and all oral medications were packaged in 7-day blister packs. For those randomized to DOT, participants punched out medication from the blister pack in front of OTP nurses. Because DOT of HCV medications was linked to OTP methadone visits, the number of directly observed oral doses varied according to the number of days the participant attended the OTP to obtain methadone. The nonobserved doses were packaged in electronic blister packs as take-home doses for self-administration on non-OTP pick-up days.

Daily adherence is defined as the percentage of days that medication was taken over the total treatment regimen; subjects receive credit only if medication is popped out of the electronic blister pack within the prescribed day. We determined the minimum adherence threshold needed to reach an SVR rate of 99%. We chose a conservative SVR rate of 99% given that the SVR rate for the ION-1 study of 12 weeks of sofosbuvir/ledipasvir was 99% [8]. As such, it is clinically relevant to understand the minimum adherence needed to reach an SVR rate comparable to that of large registration trials. We also computed SVR rates for each adherence interval with a width of 5% from 40% adherence to 100% adherence (ie, <40%, 40%–44.9%, 45%–49.9%, etc.) and computed cumulative SVR rates for participants below each adherence threshold from 40% to 100% (Figure 1). We then conducted a sensitivity analysis for which we restricted the population to only those on all-oral DAAs: sofosbuvir/ledipasvir or sofosbuvir/simeprevir (n = 113).

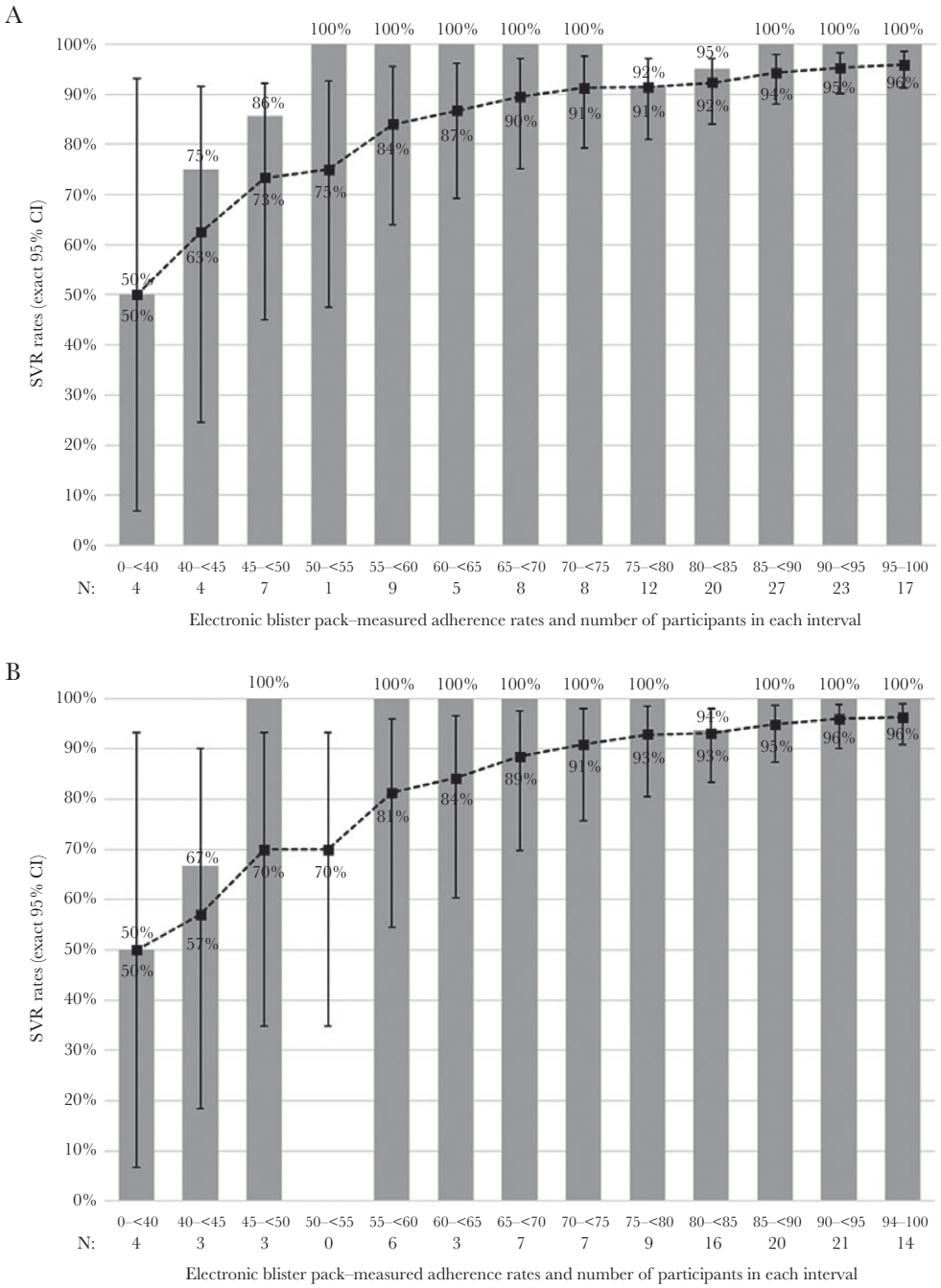

Figure 1. Sustained virologic response (SVR) rates by medication adherence rates. A, SVR rates by medication adherence rates for all participants (n = 145). B, SVR rates by medication adherence rates for only those on all oral direct-acting antivirals (n = 113).

RESULTS

The mean age (SD) was 51 (10.6) years. The majority were male (64%), Hispanic (57%), unemployed (81%), and genotype 1a (86%). The majority of participants had used drugs in the last 6 months (64%)—most commonly opiates (46%) or cocaine (47%), with 76% reporting ever injecting drugs. The majority received sofosbuvir/ledipasvir (70.3%); other regimens included sofosbuvir/simeprevir (7.6%), sofosbuvir/ribavirin (11.0%), sofosbuvir/ribavirin/pegylated interferon (9.1%), and telaprevir/ribavirin/pegylated interferon (2.1%). The overall SVR rate was 96% (95% Clopper-Pearson CI, 91%–98%), and overall daily adherence was 78% (95% CI, 76%–81%). Of the 9 participants who failed treatment, 2 died, 3 discontinued treatment before completion, and 4 had virologic failures. Factors significantly associated with poorer daily adherence were psychiatric illness at baseline (P = .048) and drinking alcohol to intoxication in the 30 days before baseline (P = .028). Drug use was not significantly associated with poor adherence. The

cumulative SVR rates with increasing adherence thresholds are presented in Figure 1. Our results for all participants demonstrate that those who achieved at least 50% adherence had an overall SVR rate of 99%, and each 5% adherence interval above 50% achieved at least 90% SVR. The minimal threshold of adherence needed to reach a 99% SVR rate was even lower when we restricted the participants to those who had received all-oral DAAs; here, those who achieved at least 45% adherence had an overall SVR rate of 99%, and each 5% adherence interval above 45% achieved at least 90% SVR.

DISCUSSION

Our study provides the first real-world data, with sufficient adherence variability, to define HCV adherence thresholds. We demonstrate that lower medication adherence may still lead to HCV cure in the era of DAAs. While in the interferon era adherence <80% has been shown to decrease rates of SVR, adherence thresholds in the DAA era have not been established [9]. In our study, among those with >50% adherence, 99% achieved HCV cure; this adherence threshold was comparable when we restricted our analysis to only those on all-oral DAAs. Furthermore, the majority of PWID with adherence <50% were also able to achieve HCV cure.

Currently, most clinicians are unaware of the optimal rate of adherence to achieve acceptable HCV cure rates in the DAA era. In clinical practice, many providers discontinue HCV treatment for patients who have poor adherence. In this study, we found that suboptimal adherence may not lead to HCV virologic failure in the era of DAAs. Although in the parent study greater adherence was significantly associated with SVR, with the odds of SVR being 1.81 times higher for each 10% increase in daily adherence (95% CI, 1.06–3.11; P = .030), these data demonstrate that participants with adherence rates <50% are the main contributors to lower SVR rates.

In other studies of PWID, adherence measured by electronic pillboxes (MEMS) or electronic blister packs has been high (>95%). Though it is reassuring that PWID can achieve high adherence, these studies did not have enough adherence variability to define lower thresholds that may still lead to SVR. Importantly, in the SIMPLIFY study, 88% of participants missed at least 1 dose of therapy, and participants defined as nonadherent (<90% adherence) did not have lower cure rates. In 11% of participants who missed >7 consecutive days of medication, none had virologic failure. Given these findings, high levels of adherence may not be necessary to achieve cure in the DAA era. Based on our study, the majority may achieve HCV cure even if only 50% adherent. One limitation is that our sample size at lower adherence rates was smaller, although there were still 15 participants with adherence <50% and 38 participants with adherence <70%.

Though efforts should be made to improve patient adherence while on HCV treatment, these data should encourage clinicians to continue with treatment in PWID even if adherence is poor. If payors and providers refuse PWID highly effective DAA medications due to adherence concerns, elimination of HCV will not be possible. These data support HCV treatment for all PWID.

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Patient consent. All participants signed written informed consent, and the study was approved by the Einstein College of Medicine Institutional Review Board.

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