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Perspectives on Adherence From the ACTG 5360 MINMON Trial: A Minimum Monitoring Approach With 12 Weeks of Sofosbuvir/Velpatasvir in Chronic Hepatitis C Treatment

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Background. With the advent of efficacious oral direct-acting antivirals (DAAs) for hepatitis C virus (HCV), identification of characteristics associated with adherence is critical to treatment success. We examined correlates of sub-optimal adherence to HCV therapy in a single-arm, multinational, clinical trial.

Methods. ACTG A5360 enrolled HCV treatment-naive persons without decompensated cirrhosis from 5 countries. All participants received a 12-weeks course of sofosbuvir/velpatasvir at entry. In-person visits occurred at initiation and week 24, sustained virologic response (SVR) assessment. Adherence at week 4 was collected remotely and was dichotomized optimal (100%, no missed doses) versus sub-optimal (<100%). Correlates of sub-optimal adherence were explored using logistic regression.

Results. In total, 400 participants enrolled; 399 initiated treatment; 395/397 (99%) reported completing at week 24. Median age was 47 years with 35% female. Among the 368 reporting optimal adherence at week 4 SVR was 96.5% (95% confidence interval [CI] [94.1%, 97.9%]) vs 77.8% (95% CI [59.2%, 89.4%]) *P* value < .001. In the multivariate model age <30 years and being a US participant were independently associated with early sub-optimal adherence. Participants <30 years were 7.1 times more likely to have early sub-optimal adherence compared to their older counterparts.

Conclusions. Self-reported optimal adherence at week 4 was associated with SVR. Early self-reported adherence could be used to identify those at higher risk of treatment failure and may benefit from additional support. Younger individuals <30 years may also be prioritized for additional adherence support.

Clinical Trials Registration. NCT03512210.

Keywords. hepatitis C; adherence; minimum monitoring; health system capacity; remote patient contact.

BACKGROUND

In the past 2 decades, treatment options for hepatitis C virus (HCV) have evolved with significant improvements in outcomes. Direct-acting antivirals (DAAs) for HCV have transformed care for persons with HCV globally [1]. This breakthrough has not impacted global populations equitably. The cost of treatment with DAAs is still a barrier to treatment access worldwide with even certain states in the United States having administrative barriers to treatment access [2–4]. ACTG 5360 "THE MINMON" trial was designed to reduce in-person clinic visits, monitoring, and testing associated with HCV therapy [5].

In most low- and middle-income countries (LMICs) the World Health Organization (WHO) backed voluntary license agreements addresses barriers associated with cost of DAA to variable degrees [6].

The rationale for the MINMON approach was to remove other cost barriers and improve treatment access by reducing costly diagnostics to help improve global treatment uptake. This was based on the hypothesis that reducing treatment monitoring would not significantly impact safety, adherence, and sustained virologic response (SVR). A prior study using real world evidence (RWE) from HCV patients in 34 academic centers and community clinics in Italy showed high levels of SVR even with lower levels of adherence [7]. An analysis of the US Veterans Health Administration database had similar findings. In those treated with sofosbuvir based regimens SVR was not significantly different in those who only received

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50% of the recommended treatment compared to full course treatment [8].

MINMON was unique in enrolling participants from 5 countries on 4 continents. The trial also enrolled people with human immunodeficiency virus (HIV, PWH) and people who used drugs (PWUD), both important populations either poorly represented or excluded from earlier simplification studies [9, 10].

In this analysis, we examined the associations of self-reported adherence with SVR, and correlates of sub-optimal adherence.

METHODS

Trial Design

ACTG 5360 (ClinicalTrials.gov: NCT03512210) was a phase IV open label, single arm trial designed to evaluate the efficacy and safety of a minimal monitoring strategy for HCV treatment. The trial enrolled treatment-naive participants without decompensated cirrhosis from 5 countries. The design eliminated on-treatment study visits, laboratory monitoring, and in-person adherence assessments. In addition, the use of sofosbuvir/velpatasvir (SOF/VEL), a pangenotypic DAA pre-treatment genotyping, was not required. FIB-4 score was used for liver disease staging, and Child-Turcotte-Pugh (CTP) classification to distinguish between compensated and decompensated cirrhosis in those with FIB-4 >3.25. After screening, participants received all 84 tablets of SOF/VEL in three 28 pill bottles; the first dose was observed. Participants were asked for preferred mode of contact including the following: telephone, text message, email, and WhatsApp (a social media platform). Because of the minimal monitoring design, evaluations of adherence such as pill counts, or electronic pill bottle monitoring were not used. Adherence and tolerability were assessed using a standardized questionnaire during treatment. At week 4, participants were asked; "during the past 4 weeks, how much of the study medication did you take?" Available responses were "All, Most, Some, or None" (Supplementary documents). At week 22 participants were contacted to schedule their week 24 SVR visit and were asked to update their preferred modes of contact. At the week 24 visit, participants were asked on what date they completed the 84-pill regimen. The trial protocol was approved by the institutional review boards/Ethics Committees of all participating sites.

Trial Population

Participants were enrolled from 38 sites in the United States, Brazil, South Africa, Thailand, and Uganda. PWH and PWUD were included. Individuals with decompensated cirrhosis, active hepatitis B virus (HBV) coinfection based solely on a positive HBV surface antigen (HBsAg), or who were pregnant, or breast-feeding were excluded. For a more detailed trial description and the full list of inclusion and exclusion criteria see the primary manuscript and the full protocol (Supplementary documents) [5].

Outcome Measures

Self-reported adherence was collected remotely at 2-time points, week 4 and week 24 (at SVR evaluation, scheduled 24 weeks from treatment initiation). Since very few participants reported variations of imperfect adherence this outcome was dichotomized (Supplementary Table 3). At week 4, self-reported adherence categories were dichotomized into "early optimal adherence" (participants reporting 100% SOF/VEL) versus "early sub-optimal adherence'(participants reporting <100% SOF/VEL). Those with missing week 4 adherence information were excluded from early optimal adherence analyses. At the week 24 visit, timely treatment completion was defined as completing all 84 tablets of SOF/VEL within 84 ± 7 days based on date of last tablet reported. A composite measure of adherence; "overall optimal adherence" was defined as taking all medications at week 4 and completing treatment in a timely manner. In sensitivity analyses, participants who had missing week 4 adherence information at week 4 were classified as early having sub-optimal adherence, and participants who failed to return for week 24 were classified as having overall sub-optimal adherence.

Adherence was compared within the following subgroups: <30 years of age versus ≥30 years, sex at birth, gender identity, time since HCV diagnosis (≤1 year vs >1 year), stability of participant preferred contact information, non-antiretroviral (ART) polypharmacy (> 5 medications), currently prescribed mental health medication, country, and HIV disease status, drug injection, alcohol, cannabis, and other illicit substances. SVR was defined as plasma HCV RNA less than the lower limit of quantification of the assay measured at least 22 weeks post-treatment initiation (and up to 76 weeks). Missing HCV RNA result was defined as SVR non-response (ie, missing = failure).

Statistical Analysis

As specified by the primary analysis plan SVR was estimated within groups defined by adherence using the method of binomial proportions and nominal, 2-sided, 95% confidence intervals (CI) using Wilson score method. Correlates of early sub-optimal adherence, and separately overall sub-optimal adherence were each investigated using multi-variate logistic regression. Covariates with a P value <.20 from the global Wald χ^2 test in univariate models were included in multivariate logistic regression modeling utilizing exact methods, if necessary, for sparse data, and a stepwise selection approach with an entry P value of .10 and a selection level of .05. Two-way statistical interactions between covariates in the resulting multivariate model were explored. All statistical analyses were performed using SAS version 9.4 (SAS institute, Cary, North Carolina, USA).

RESULTS

Adherence to HCV Treatment by Selected Baseline Characteristics

Between October 2018 and July 2019, 400 participants enrolled (and 399 initiated treatment) from 38 sites in 5 countries on 4 continents; Brazil (n = 2), USA (n = 31), Uganda (n = 1), South Africa (n = 2), and Thailand (n = 2). The median age of the participants was 47 years (IQR: 37, 57), 35% were female sex assigned at birth, with 6% self-identifying gender identity as non-cisgender. Forty-one percent of participants were coinfected with HIV, and 14% reported current substance use at baseline. Four individuals who could not be contacted at week 4 were excluded from the analysis of early adherence and considered to have sub-optimal overall adherence. Among the 4 participants, 1 was lost to follow-up, 1 did not complete treatment in a timely manner, that is, within 84 ± 7 days and the other 2 had timely treatment completion. Self-reported early optimal adherence by remote contact was high; 368/395 (93%) reported perfect adherence (taking 100% SOF/VEL at week 4 (Table 1 and Supplementary Tables). Early optimal adherence ranged from 84% (108 of 128) participants in the United States, 87% (13 of 15) in Uganda, 98% (127 of 130) in Brazil, 98% (108 of 110) in Thailand, to 100% (12 of 12) in South Africa.

Within subgroups, the lowest reported early optimal adherence was among individuals <30 years (24 of 32) (75%), those with ongoing psychoactive medication use (52 of 60) (87%), and those who reported current injection drug use (13 of 15) (87%). Using the overall optimal adherence measure, 22 of 31 (71%) of the under 30-year-old age group reported overall optimal adherence and 324 of 361 (90%) among those 30 or older. Self-reported early optimal adherence and the combination of week 4 optimal adherence and retrospective report of timely completion at week 24 overall optimal adherence, by different subgroups, are shown in Table 1.

Ninety four percent, that is, 154 of the 163 PWH reported early optimal adherence; this was similar to those without HIV (214 of 232) (92%). There was no difference in SVR by HIV status. Current alcohol use was reported by 40% of the study population, with 11 reporting daily use. Early optimal adherence was reported by 144 of 157 (92%) of current alcohol users and 222 of 236 (94%) of past and non-users of alcohol. All 11 individuals reporting daily alcohol use reported early optimal adherence to DAAs.

Reasons for Sub-Optimal Adherence in MINMON

Reasons for sub-optimal adherence were collected at week 4 by remote contact and at the SVR visit. Reponses were entered into the study database, during analysis similar responses were combined. Among the 27 individuals who reported early sub-optimal-adherence, 16 (59%) endorsed forgetting to take medications and 4 (15%) endorsed not having their medications with them (Supplementary Table 4). The protocol offered replacement for lost medications if reported within 14 days of loss. Three participants reported losing their DAAs: 2 of these cases occurred in the final month of treatment and the last bottle in both cases were replaced following timely reporting; 1 case occurred during the first month of treatment and was not reported promptly and thus not replaced. This participant only completed 6 days of SOF/VEL therapy and was considered <100% adherent. The 2 individuals who reported losing their last bottles both reported 100% adherence at week 4; 1 completed treatment within 91 days, the other participant's last dose was at day 95, both achieved SVR.

Sustained Virologic Response

355 of 368, (96.5%) reporting early optimal adherence at week 4 achieved SVR: compared to 21 of 27 (77.8%) reporting early sub-optimal-adherence P value <.001 (Figure 1). A sensitivity analysis of SVR was done classifying the 4 individuals who could not be reached at week 4 as non-adherent. The sensitivity analysis results were similar with a SVR estimate of 96.5% for optimal adherence versus 77.5 for sub-optimal P value <.001. When considering adherence over the whole treatment period; those with optimal overall adherence, 334 of 346 (96.5%) achieved SVR compared to 42 of 46 (91.3%) reporting sub-optimal adherence. (P-value = .1).

Correlates of Early Optimal Adherence

Adherence was lower among the US participants compared to other regions (Table 1); 84% of US participants at week 4% and 79% for overall optimal adherence. In the adjusted analysis, participants in Thailand, Brazil, South Africa, and Uganda reported higher levels of optimal adherence at week 4 compared to the those in the United States (P value <.01) (Figure 2). For individuals <30 years old, optimal adherence was significantly lower for both early and overall adherence, even after controlling for geographic location (Table 2). Among those reporting current substance use, overall optimal adherence was significantly lower (P value = .03) while the difference in early optimal adherence was not significant (P value = .16). Reported early optimal adherence levels were still relatively high, at least 87%, regardless of self-reported history of substance use (Figure 3). The adjusted correlates model showed that individuals <30 years were 7.1 times as likely to have early sub-optimal adherence compared to older participants.

DISCUSSION

MINMON demonstrated that high levels of adherence and SVR could be achieved using a minimal monitoring design with only 2 in-person visits. In this analysis we showed that remotely captured self-reported early optimal adherence at week 4 was associated with SVR. Individuals reporting early optimal adherence had an SVR of 96.5% compared to 77.8% for those

Table 1. Participant Characteristics at Baseline by Adherence Status Based on Week 4 Adherence and Overall Adherence Based on Week 4 Status and Retrospective Timely Treatment Completion

	Remotely Obtained on Treatment Adherence at Week 4 (Early Adherence)			Overall Adherence Based on Remotely Obtained Week 4 and Timely Treatment Completion (Overall Adherence)		
Participant Characteristics	N	Self-reported 100% SOF/VEL (Optimal Adherence) n/N (%)	Self-reported <100% SOF/VEL n/N (%)	N	100% Week 4 Adherence and Timely Treatment Completion (Overall Optimal Adherence) n/N (%)	<100% Week 4 Adherence and or Non-timely Treatment Completion (Overall Sub-optimal Adherence) n/N (%)
Total Sample	395	368	27	392	346	46
Country						
Brazil	130	127 (98)	3 (2)	130	120 (92)	10 (8)
South Africa	12	12 (100	0 (0)	12	10 (83)	2 (17)
Thailand	110	108 (98)	2 (2)	110	104 (95)	6 (5)
US	128	108 (84)	20 (16)	125	99 (79)	26 (21)
Uganda	15	13 (87)	2 (13)	15	13 (87)	2 (13)
Age at enrollment						
<30 y	32	24 (75)	8 (25)	31	22 (71)	9 (29)
≥30 y	363	344 (95)	19 (5)	361	324 (90)	37 (10)
Sex at birth						
Female	138	130 (94)	8 (6)	136	123 (90)	13 (10)
Male	257	238 (93)	19 (7)	256	223 (87)	33 (13)
Gender identity						
Cisgender	374	348 (93)	26 (7)	371	327 (88)	44 (12)
Transgender spectrum	21	20 (95)	1 (5)	21	19 (90)	2 (10)
Time from HCV diagnosis						
≤1 y	110	99 (90)	11 (10)	110	95 (86)	15 (14)
>1 y	285	269 (94)	16 (6)	282	251 (89)	31 (11)
HIV status						
HIV-1 not present	232	214 (92)	18 (8)	229	200 (87)	29 (13)
HIV-1 present	163	154 (94)	9 (6)	163	146 (90)	17 (10)
Self-reported IDU status						
Current	15	13 (87)	2 (13)	15	10 (67)	5 (33)
Previous	120	109 (91)	11 (9)	118	104 (88)	14 (12)
Never/not evaluated	260	246 (95)	14 (5)	259	232 (90)	27 (10)
Self-reported Alcohol use						
Current, daily	11	11 (100)	0 (0)	11	10 (91)	1 (9)
Current, not daily	146	133 (91)	13 (9)	145	125 (86)	20 (14)
Previous/never	236	222 (94)	14 (6)	234	209 (89)	25 (11)
Not evaluated	2	2 (100)	0 (0)	2	2 (100)	0 (0)
Self-reported cannabis use						
Current/previous	190	169 (89)	21 (11)	187	159 (85)	28 (15)
Never/not evaluated	205	199 (97)	6 (3)	205	187 (91)	18 (9)
Self-reported substance use[a]						
Current	54	49 (91)	5 (9)	53	42 (79)	11 (21)
Previous/never/not evaluated	341	319 (94)	22 (6)	339	304 (90)	35 (10)
Ongoing psychoactive medication use[b]						
Yes	60	52 (87)	8 (13)	58	46 (79)	12 (21)
No	335	316 (94)	19 (6)	334	300 (90)	34 (10)
Non-ART polypharmacy[c]						
≥5 Medications	55	51 (93)	4 (7)	54	46 (85)	8 (15)
<5 medications	340	317 (93)	23 (7)	338	300 (89)	38 (11)

In this table individuals with missing data on adherence at week 4 remote contact and treatment completion are excluded.

Abbreviations: ART, antiretroviral therapy; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HIV-1, human immunodeficiency virus type 1; IDU, injection drug use; SOF/VEL, sofosbuvir/velpatasvir.

[a]Drug use was collected using the World Health Organization (WHO) Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) Questionnaire. Current use is defined as self-reported use at least once in the past 3 months prior to study entry. Substance use defined as any current or previous usage of amphetamines, hallucinogens, cocaine, opioids, or sedatives. Two participants were not evaluated for drug use at study entry due to site error and participant declining.

[b]Ongoing psychoactive medication use was defined as use of any medication prescribed for any diagnosis. Anti-addiction and anticonvulsant medications are excluded from psychoactive medications.

[c]Prophylaxis for HIV is included as 1 medication; antiretrovirals (ARVs) are excluded from non-ART polypharmacy.

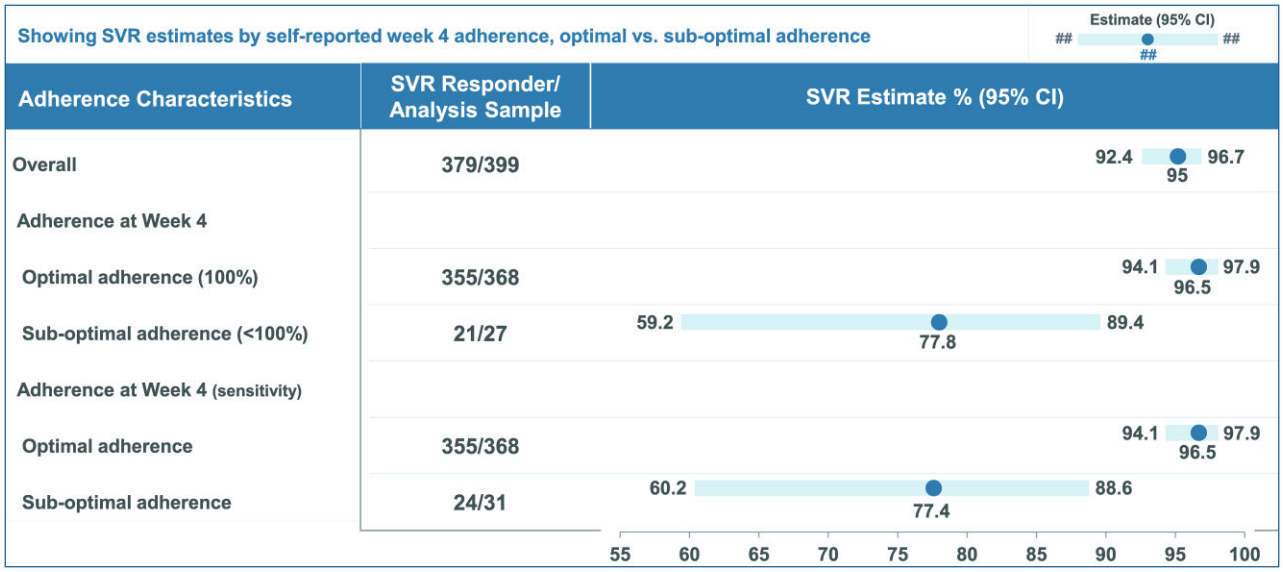

Figure 1. Showing SVR estimates by self-reported week 4 adherence, 100% versus <100%. Self-reported sub-optimal adherence at week 4 was highly predictive of treatment failure. In this study adherence data were collected by self-report, information collected was not confirmed by pill count or any other validated means of adherence determination. SVR was 96.5% (95% CI: [94.1–97.9]) in those reporting sub-optimal adherence at week 4 versus 77.8% (95% CI: [59.2–89.4]) for those reporting sub-optimal ($P < .001$). The upper estimate excluded those who could not be reached at week 4 from analysis and the lower estimate assumed they were non-adherent. The result was unchanged even after including those who could not be reached at week 4 remote contact as non-adherent. Abbreviations: CI, confidence interval; SVR, sustained virologic response.

reporting early sub-optimal adherence An analysis of RWE across 34 academic and community centers in Italy on 365 HCV patients without advanced fibrosis by Fabbiani et al [7] reported similar results, with an SVR of 99.1% in patients who completed ≥4 weeks of DAAs versus 50% in those with <4 weeks; $P = .003$. These results suggest early treatment adherence in HCV treatment is critical for treatment success. Another study on intrahepatic viral kinetics during HCV treatment in genotype 1a patients using paritaprevir/ritonavir, ombitasvir, dasabuvir, plus ribavirin revealed rapid viral clearance in >90% of infected hepatocytes in the first 7 days of DAA treatment [11]. These findings suggest patients might benefit from interventions focused on maximizing adherence during the first weeks of treatment.

In MINMON, the proportion of individuals who reported completing treatment was high and comparable to other studies (96%–99%) [12, 13]. The high SVR observed among those reporting sub-optimal adherence mirrors RWE suggesting that successful treatment with potent DAAs may be achieved with lower levels of adherence[7, 14–16]. This was seen in the SIMPLIFY study, a trial among recent people who inject drugs (PWID). Another secondary analysis of pooled data from 8 phase 3 clinical trials using the pangenotypic DAA glecaprevir/pibrentasvir with a sample size of 2091 confirmed this finding. In this study any history of alcohol use was associated with a odds ratio of 2.38 (95% CI 1.13–5.01) of being non-adherent to HCV therapy [17]. Among those who were non-adherent SVR was 87% compared with 98% for those who were adherent ($P < .001$). Our results and prior studies support a global implementation of HCV treatment using less intense monitoring, with a focus on viral hepatitis C elimination. The minimal monitoring approach tested in MINMON is especially suited for LMIC settings with limited provider and health system capacity, similar models have been used in countries like Egypt and Australia [18, 19]. The model also has some intrinsic adherence benefits—the provision of all 84 tablets on day 1 reduced the risk of non-adherence from prescription refill delays and other logistical barriers impacting medication availability. The use of multiple means of contacting participants probably improved the ability to reach participants leading to better engagement and thus improved ability to ascertain SVR.

The 95% SVR of MINMON and high levels of adherence with a cost sensitive client-centered strategy questions the utility of costly, time and resource intensive adherence monitoring and interventions utilized in prior HCV treatment protocols and programmatic rollouts. In MINMON, a low contact reduced monitoring approach to HCV treatment, self-reported week 4 optimal adherence was high even in those reporting substance use (Figure 3). The high rate of optimal adherence (> 87%) in all substance use categories challenges the utility of administrative barriers to treatment access based on substance use used in some jurisdictions [20, 21]. Remote participant adherence using varied modes of contact based on individual preference appeared effective in maintaining high levels of adherence and

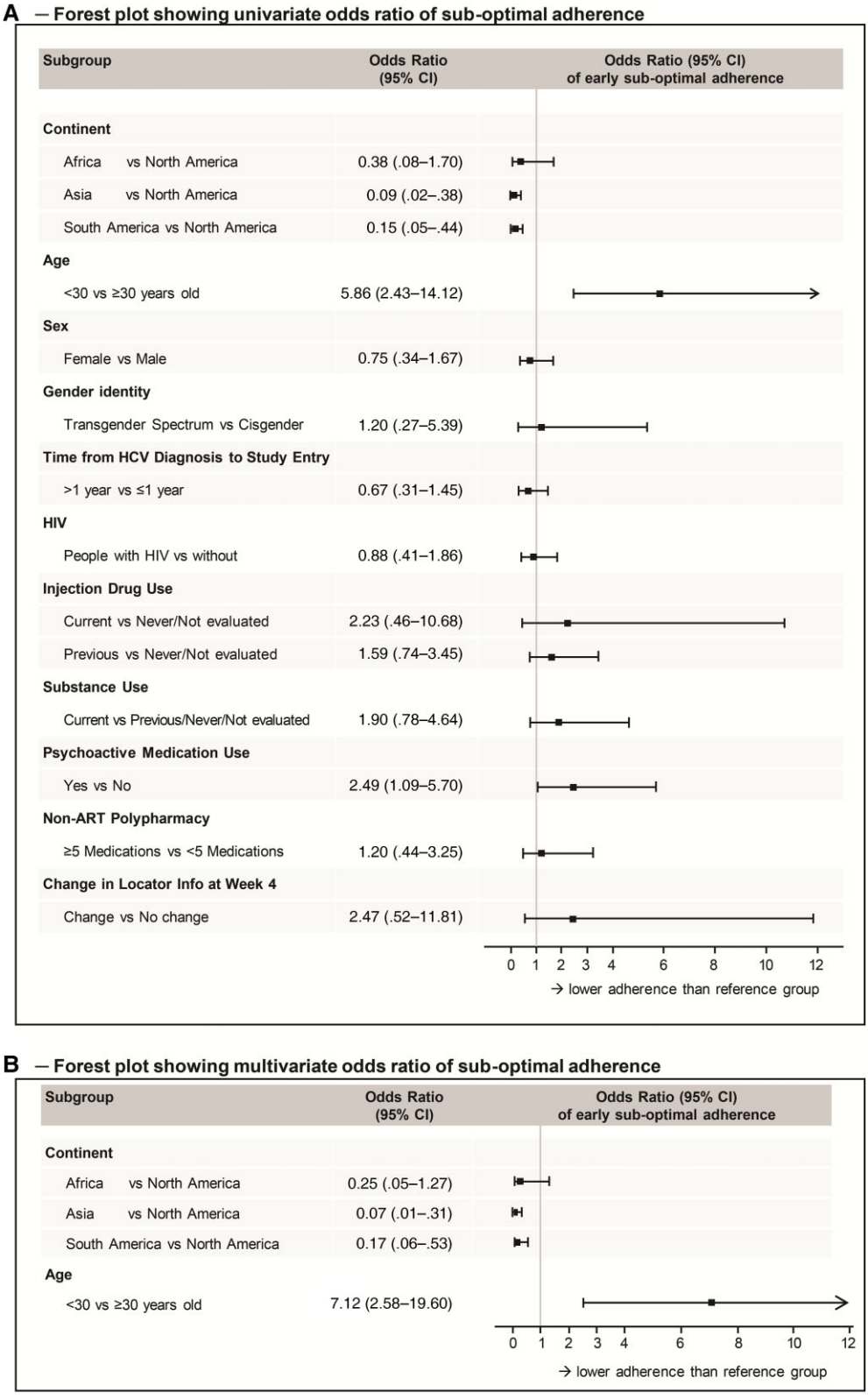

Figure 2. Showing univariate and adjusted odds of early sub-optimal adherence by participant characteristics. Univariate analysis (*A*) suggests that younger individuals <30 years at time of enrollment, participants in the United States and those with current psychoactive prescriptions were more likely to have early sub-optimal adherence. In the adjusted correlates model (*B*) only age and geographic location were associated with early sub-optimal adherence. On account of variations in health systems and hepatitis C access by country and region the significantly reduced adherence in US/North American partcipants is difficult to interpret. In this figure Africa is the combination of participants from South Africa and Uganda, United States is the only country in North America, Brazil is the only country in South America, and Thailand represents Asia. Abbreviations: CI, confidence interval; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

Table 2. Table of Univariate and Multivariate Odds Adherence by Selected Baseline Characteristics in an HCV Simplification Regimen Based on the Outcome of Sub-optimal Adherence (<100% Adherence) at Week 4 and Overall Adherence a Combined Measure of Week 4 Adherence Status and Retrospective Timely Treatment Completion

Baseline Characteristics	Univariate Odds Ratio of Early Sub-optimal Adherence (<100% Adherence at Week 4 [95% CI])	*P* value	Multivariate Odds Ratio of Early Sub-optimal Adherence (<100% Adherence at Week 4 [95% CI])	*P* value	Univariate Odds Ratios of Overall Sub-optimal Adherence (95% CI)	*P* value	Multivariate Odds Ratio of Overall Sub-optimal Adherence (95% CI)	*P* value
Region								
Sub-Saharan Africa (South Africa and Uganda) vs US	0.38 (.08–1.70)	<0.01	0.25 (.05–1.27)	<.01	0.54 (.17–1.67)	< .01	0.49 (.15–1.60)	< .01
Asia (Thailand) vs US	0.09 (.02–.38)		0.07 (.01–.31)		0.18 (.07–.45)		0.17 (.07–.44)	
South America (Brazil) vs US	0.15 (.05–.44)		0.17 (.06–.53)		0.28 (.14–.59)		0.33 (.16–.70)	
Age category								
< 30 y vs ≥30 y	5.86 (2.43–14.12)	<.01	7.12 (2.53–19.60)	<.01	3.86 (1.75–8.52)	< .01	4.38 (1.83–10.50)	<.01
Sex at birth								
Female vs male	0.75 (.34–1.67)	.48			0.78 (.42–1.47)	.45		
Gender identity								
Transgender spectrum vs cisgender	1.20 (.27–5.39)	.81			1.03 (.29–3.62)	.96		
Number of years from HCV diagnosis								
>1 y vs ≤ 1 y	0.67 (.31–1.45)	.31			0.96 (.50–1.82)	.90		
HIV coinfection status								
HIV vs non-HIV	0.88 (.41–1.86)	0.73			0.83 (.46–1.51)	.54		
Self-reported IDU[a]								
Current vs never/not evaluated	2.23 (.46–10.68)	.37			3.74 (1.20–11.67)	.07		
Previous vs never/not evaluated	1.59 (.74–3.45)				1.22 (.65–2.31)			
Self-reported substance use[a]								
Current vs previous/never/not evaluated	1.90 (.78–4.64)	.16			2.60 (1.30–5.18)	<.01	2.23 (1.07–4.63)	.03
Self-reported daily alcohol use								
Current daily use vs non-daily use[b]					0.65 (.08–5.15)	.68		
Ongoing psychoactive medication use[c]								
Yes vs no	2.49 (1.09 -5.70)	.03			2.57 (1.31–5.05)	<.01		
Non-ART polypharmacy[d]								
≥5 vs <5 medications	1.20 (.44–3.25)	.73			1.52 (.71–3.23)	.28		
Change in locator info at Week 4								
Change vs stable	2.47 (.52–11.81)	0.26			1.43 (.24–8.64)	0.70		

All those with missing information due to inability to contact and or loss to follow up are included in the non-optimal adherence groups.

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDU, injection drug use.

[a]Drug use was collected using the World Health Organization (WHO) Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) Questionnaire. Current use is defined as self-reported use at least once in the past 3 months prior to study entry. Substance use defined as any current or previous usage of amphetamines, hallucinogens, cocaine, opioids, or sedatives. Two participants were not evaluated for drug use at study entry due to site error and participant declining.

[b]Alcohol use was not included in the week 4 adherence odds because no participants with <100% adherence reported daily alcohol use.

[c]Ongoing psychoactive medication use was defined as use of any medication prescribed for any diagnosis. Anti-addiction and anticonvulsant medications are excluded from psychoactive medications.

[d]Prophylaxis for HIV is included as 1 medication; antiretrovirals (ARVs) are excluded from non-ART polypharmacy.

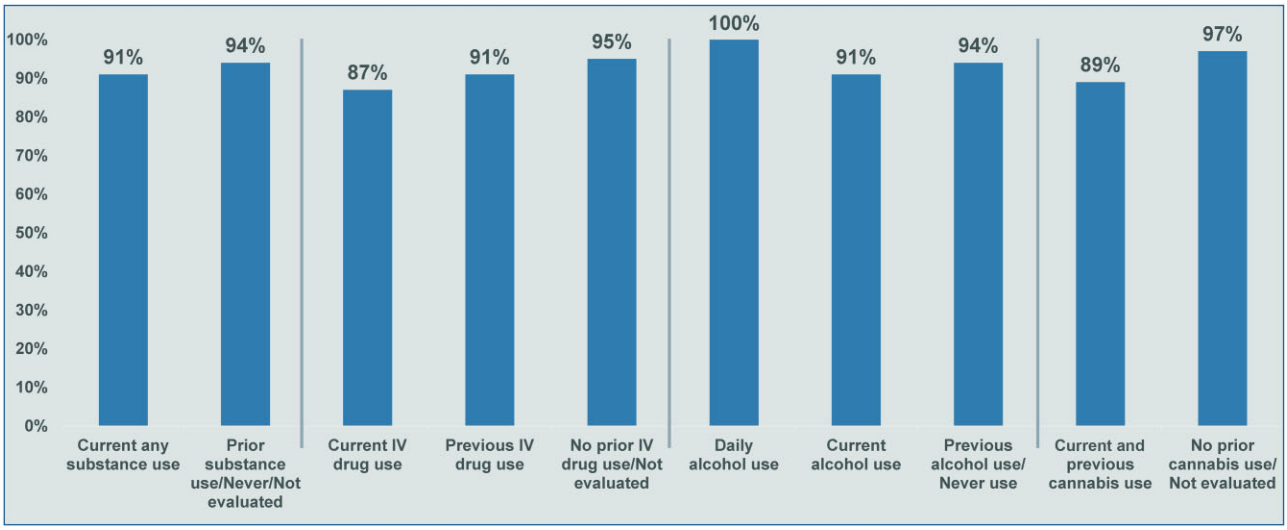

Figure 3. Showing optimal adherence at week 4 by different categories of substance use. Substance use in this study was collected at baseline and screening using questionnaires. All data on substance use were obtained by participant self-report. No attempt was made to confirm this with urine or serum substance abuse testing. Drug use was collected using the WHO ASSIST Questionnaire. Alcohol use history was collected using a modified AUDIT screening tool. The most common substance used other than tobacco was alcohol, 85% of all participants reported either current or prior use. Other substances reported were, cannabis, 48%, cocaine 37%, amphetamines 32%, opioids 25%, sedatives 19% and other hallucinogens 20%. These percentages include both prior and current use. For all the substances current use is defined as any use within the past 3 months. Daily use data were only collected on alcohol on account of known recommendations by some prior and current treatment guidelines suggesting possible association with poor SVR adherence and SVR outcomes. All daily alcohol users reported 100% adherence at week 4. This finding must be interpreted with caution as the numbers were small, only 11 participants reported daily alcohol use, for detailed numbers see Table 1. This chart only includes data on individuals with adherence data from week 4 remote contact. Abbreviations: ASSIST, Alcohol, Smoking and Substance Involvement Screening Test; AUDIT, Alcohol Use Disorders Identification Test; IV, intravenous; SVR, sustained virologic response; WHO, World Health Organization.

study retention in both the US and LMIC settings. Optimal adherence was lower for US participants compared to non-US groups, but no significant difference in SVR was noted. The lower level of adherence in US participants may be secondary to higher likelihood of selection of highly motivated patients in LMICs with relative lack of access to HCV DAAs compared to the United States during the study period (2018/2019). Differences in cultural acceptability of reporting non-adherence may have played a role in the observed results.

MINMON showed that self-reported optimal adherence at week 4 was highly predictive of SVR. Not all studies have found correlations with adherence and SVR with DAA therapy for HCV. Some prior studies found early treatment discontinuation to be the strongest predictors of not achieving SVR [22, 23]. In SIMPLIFY almost all participants who completed treatment achieved SVR, except for 3, 2 of whom were lost to follow-up and 1 who did not have a sample taken at end of treatment [15]. This result almost mirrors MINMON, with 99% completing treatment, and returning for SVR evaluation, except for 3, 2 were lost to follow-up and 1 had a sample taken prior to the protocol defined SVR evaluation window.

Our multivariate model identified age <30 years as one of the most important predictors of self-reported sub-optimal adherence. The finding of lower treatment adherence in younger patients has been reported in other studies including among patients with HIV and type I diabetes [24, 25]. Other than country of residence, none of the other variables, such as sex at birth, HIV status, history of substance abuse, daily alcohol or marijuana use were shown to be independently associated with non-adherence.

The data suggest that younger persons, that is, <30 years could be prioritized for adherence interventions to maximize SVR. Strategies such as treatment adherence applications which provide reminders, use of peer mentors and mobile phone-based counseling interventions which have been used in PWH could be utilized in such populations [26, 27].

Limitations of This Analysis

These findings need to be interpreted with caution. Many of the LMICs in this trial had very limited access to DAAs possibly allowing selection of more motivated participants. With the minimal monitoring nature of the intervention, no direct measures (such as pill count or directly observed therapy [DOT]) for collecting adherence data nor any electronic adherence monitoring were used. All adherence data were based on self-report and as such may be subject to memory and recall bias. Because Week 4 adherence data were captured in real-time, this outcome may be less subject to retrospective bias. Week 4 adherence is based on each participant's response to questionnaire and relies on the participant's understanding of the

question and self-report, which is often subject to a ceiling effect. In our regression analysis some of the subgroups were small, and associations between OPTIMAL adherence and SVR were sensitive to how the small numbers of participants stopping treatment early and/or missing data were handled.

CONCLUSION

Treatment barriers continue to limit uptake of HCV treatment in both high income and LMIC. A minimal monitoring approach with only 2 in-person visits, reduced laboratory testing, and a week 4 adherence assessment had high treatment completion and SVR. The remotely obtained week 4 adherence was a strong predictor of SVR. Implementing the MINMON strategy may overcome many of the structural barriers impeding access to HCV treatment globally. Treatment programs should consider incorporating early remote adherence assessment and providing additional support for those reporting suboptimal adherence. Younger individuals (<30 years), and individuals with current prescriptions of psycho-active drugs may benefit from additional adherence support.

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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