

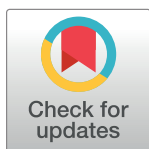
RESEARCH ARTICLE

The Alaska Native/American Indian experience of hepatitis C treatment with sofosbuvir-based direct-acting antivirals

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Abstract

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Background

Direct-acting antiviral (DAA) drugs have been effective in the treatment of chronic hepatitis C virus (HCV) infection. Limited data are available on safety, tolerability, and efficacy in American Indian or Alaska Native people. We aim to evaluate the treatment outcomes of sofosbuvir-based regimens for treatment of HCV in a real life setting in Alaska Native/American Indian (AN/AI) people.

Methods

AN/AI patients within the Alaska Tribal Health System with confirmed positive anti-HCV and HCV RNA, who were 18 years of age and older were included in the study. Pretreatment baseline patient characteristics, treatment efficacy based on sustained virologic response (SVR) 12 weeks after treatment completion, and adverse effects were assessed. The following treatments were given according to the American Association for the Study of Liver Diseases/Infectious Disease Society of America (AASLD/IDSA) HCV Guidance: ledipasvir/sofosbuvir, sofosbuvir plus weight-based ribavirin, and sofosbuvir/velpatasvir.

Results

We included 501 patients with a mean age of 54.3 (range 21.3–78.3) in the study. Overall SVR was achieved in 95.2% of patients who received one of the three DAA regimens. For those with cirrhosis, overall SVR was 92.8% and for those with genotype 3 91.1% achieved SVR. The most common symptom experienced during treatment was headache. Joint pain was found to decrease during treatment. One person discontinued sofosbuvir plus ribavirin due to myocardial infarction and one discontinued sofosbuvir/velpatasvir due to urticaria.

Conclusions

In the real-world setting, sofosbuvir-based treatment is safe, effective, and well tolerated in AN/AI patients. Sustained virologic response was high regardless of HCV genotype or cirrhosis status.

Introduction

Hepatitis C virus (HCV) infection is one of the main causes of chronic liver disease and liver-related death worldwide [1, 2]. The number of chronically infected individuals globally is estimated to be over 130 million [3]. Moreover, most new cases of acute HCV infection are not identified or reported to public health authorities because most adults and adolescents with HCV do not have symptoms and are unaware of their infection. The U.S. Centers for Disease Control and Prevention (CDC) estimates there were 57,500 new HCV infections in the United States in 2019 alone [4]. American Indian /Alaska Native People have the highest rates of acute HCV infection and mortality related to HCV as compared to the U.S. population overall [4]. Chronic hepatitis C is a known risk factor for development of hepatocellular carcinoma (HCC) [5]. Out of 819,400 cases of HCC that occurred worldwide in 2017, 28.6% are attributable to HCV infection [6].

The prevalence of HCV infection in the United States in 2013–2016 was reported to be 2.4 million cases, with over 30,000 new cases of HCC and approximately 27,000 deaths registered every year [7, 8]. Increasing rates of hepatitis C in Alaska have been reported however, currently rates by race are not reported by the State of Alaska [9].

The first National Viral Hepatitis Action Plan that aimed to eliminate hepatitis C was issued in 2011 [10]. It focused on hepatitis B and C elimination by the year 2020 and recognized that success of the action plan could not be achieved without input from non-federal stakeholders, both public and private. Since then, several U.S. states implemented their own hepatitis elimination programs with ambitious goals of eliminating viral hepatitis by 2030, in accordance with the World Health Organization's directive on eliminating viral hepatitis [11, 12].

A number of studies have described the epidemiology of HCV infection among American Indian or Alaska Native people [13–18]. Risk factors for acquisition of HCV infection and genotype (GT) distribution among AN/AI were similar to those found in the National Health and Nutritional Examination Survey [15, 16]. End stage liver disease (ESLD) was associated with older age and alcohol usage [18]. Previously we found that AN/AI people did not respond well to peginterferon and ribavirin-based treatment with an overall (all GTs) SVR rate of 51% and discontinuation rate of 52% [17]. Genotype 3 HCV infection was associated with a high risk for developing ESLD, HCC and liver-related death [16]. Bruden et al [18] emphasized the need for early hepatitis C treatment of patients with moderate fibrosis to prevent development of ESLD, HCC and liver-related death over time.

Alaska Native and American Indian (AN/AI) communities are one of the priority populations in the Viral Hepatitis National Strategic Plan: 2021–2025 [19]. A recent study showed that 86% of AN/AI people diagnosed with HCV infection in Alaska were linked to care and treatment in 2017 [14]. Despite that, national data show AN/AI people are disproportionately affected by hepatitis C with the highest rates of both acute HCV infection and hepatitis C-related deaths [19].

With the advent of new direct-acting antivirals (DAAs) the HCV treatment landscape has changed. Recent studies report higher efficacy, shorter treatment duration, and fewer side

effects with the inclusion of the DAA sofosbuvir into treatment regimens [20–22]. Importantly, hepatitis C DAA therapy has eliminated the GT dependent differences in effectiveness that were associated with interferon-based therapies. Public health experts now believe it is possible to eliminate the disease. Hepatitis C elimination could have a tremendous positive effect on improving health outcomes by preventing around 400,000 deaths worldwide from complications each year [23].

There remains ongoing discussion about whether the effectiveness of hepatitis C treatment varies between racial and ethnic groups in the United States [24]. Besides a study by Mera et al [25] that examined HCV treatment response in 288 American Indian/Alaska Native patients treated with DAAs in clinics participating in Extension for Community Healthcare Outcomes (ECHO), little is known about effectiveness of direct acting antivirals in Alaska Native/American Indian People. The Liver Disease and Hepatitis program (LDHP) at the Alaska Native Tribal Health Consortium (ANTHC) provides a reliable setting to study disparities in hepatitis C treatment due to high rates of the disease in Alaska [26], with an ongoing registry in place, and an established AN/AI HCV-infected cohort from a large and diverse AN/AI population.

In this study we aimed to evaluate the effectiveness of sofosbuvir-based hepatitis C treatment regimens and describe any differences in experience and outcome among AN/AI people living in Alaska as compared to other racial and ethnic groups.

Materials and methods

Study design, setting, participants and data collection

In 1995, the ANTHC LDHP began a hepatitis C population-based cohort study (AK-HEPC) to learn more about adverse outcomes of chronic HCV infection in AN/AI persons. AN/AI persons residing in Alaska can receive care through the Alaska Tribal Health System (ATHS), an integrated system of tribally-owned and operated health care organizations for which ANTHC is the umbrella organization coordinating healthcare throughout the ATHS. The LDHP operates out of the Alaska Native Medical Center (ANMC), the specialty referral hospital for the ATHS located in Anchorage, Alaska. Screening for hepatitis C is done in accordance with CDC recommendations. Statewide testing for HCV infection is provided at ANMC for AN/AI people. Screening prompts are included in the electronic health record. All persons found to be HCV antibody (anti-HCV) positive are entered into a registry for clinical care. New positive anti-HCV tests are automatically reflexed to HCV RNA testing when specimen quantity permits. Those entered into the registry are invited to join the AK-HEPC cohort study. Data from this cohort was studied from March 1, 2014 (when the first participant was recruited) through September 30, 2019 (one year after the last participant was recruited) in 501 patients with chronic HCV. Fifteen patients declined to partake in the study.

AN/AI patients within ATHS with confirmed positive anti-HCV and HCV RNA, who were 18 years of age and older, and who provided written informed consent were included in the study. The study was approved by the Alaska Area Institutional Review Board and by two Alaska Tribal Health Organizations, ANTHC and Southcentral Foundation.

Patients were excluded from the study if they had negative HCV RNA prior to treatment, current incarceration, contraindication to taking any component of a sofosbuvir-based regimen, or no indication for treatment in accordance with the American Association for the Study of Liver Diseases (AASLD) and Infectious Disease Society of America (IDSA) HCV Guidance [27].

Hepatitis C treatment options were discussed with the patient prior to consenting to the treatment study. These options included all available hepatitis C medications, not just sofosbuvir-based drugs. Early on in the DAA era when this study was conceptualized and approved,

sofosbuvir-based drugs were the most commonly used interferon-free treatments available. They were considered most appropriate for the majority of patients at that time due to their safety and side effect profiles, and thus were the first line medications used for treatment. Hepatitis C patients treated with other types of drugs were excluded from this analysis due to their small numbers. Therefore, this manuscript examines hepatitis C treatment and outcomes of patients who were treated with sofosbuvir-based drugs only.

AUDIT-C alcohol screening and PHQ-9 depression screening tests were completed by patients prior to treatment start. Those with positive AUDIT-C scores (≥ 3 for women and ≥ 4 for men) were counseled about hazardous drinking and offered referral to a behavioral health counselor as were persons with PHQ-9 scores over 9.

Treatment regimens

The Food and Drug Administration-approved sofosbuvir-based treatment regimens included in this study were ledipasvir/sofosbuvir, sofosbuvir plus weight-based ribavirin, and sofosbuvir/velpatasvir. Indications and treatment duration in accordance with prescribing information are shown in Table 1.

Due to low numbers for comparison, those with decompensated cirrhosis treated with sofosbuvir/velpatasvir for 24 weeks ($n = 1$), ledipasvir/sofosbuvir for 24 weeks ($n = 17$), sofosbuvir/velpatasvir with ribavirin for 12 weeks ($n = 6$), ledipasvir/sofosbuvir and ribavirin for 12 weeks ($n = 9$), and ledipasvir/sofosbuvir and ribavirin for 24 weeks ($n = 4$) were not included in this analysis.

Treatment protocol was the same for those who were enrolled in the study cohort and those who chose not to be in the study and based on current recommendations from the AASLD/IDSA HCV Practice Guidance [27]. All participants followed the same treatment protocol except that those treated outside of Anchorage, mostly at rural Alaska Tribal facilities, were not required to complete a symptoms inventory before and during treatment. Rural tribal health providers consulted with LDHP providers for treatment recommendations when participants were treated outside of Anchorage.

Table 1. Treatment regimens of 501 AN/AI persons treated for hepatitis C in Alaska using sofosbuvir-based direct acting antiviral therapy, Alaska (treated March 2014– December 2018).

Treatment Regimen	Duration of treatment and sample size	Indication
Ledipasvir/sofosbuvir	8 weeks ($n = 110$)	GT 1 without cirrhosis and HCV viral load < 6 million international units/mL could be given for a shortened course of 8 weeks, in accordance with prescribing information and at the discretion of the prescribing provider
Ledipasvir/sofosbuvir	12 weeks ($n = 238$)	GT 1,4,5, and 6 patients who were treatment naïve without cirrhosis or with compensated cirrhosis or GT 1,4,5, and 6 patients without cirrhosis who had previously been treated with interferon-based treatment
Sofosbuvir plus ribavirin	12 weeks ($n = 39$)	GT 2 without cirrhosis. Used until sofosbuvir/velpatasvir became available in Aug 2016
Sofosbuvir plus ribavirin	16 weeks ($n = 6$)	GT 2 with cirrhosis or previously treated with interferon-based treatment. Used until sofosbuvir/velpatasvir became available in Aug 2016
Sofosbuvir plus ribavirin	24 weeks ($n = 14$)	GT 3 regardless of cirrhosis status. Used until sofosbuvir/velpatasvir became available in Aug 2016
Sofosbuvir/velpatasvir	12 weeks ($n = 94$)	All GTs without cirrhosis or with compensated cirrhosis starting in Aug 2016

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Study assessments

Pre-treatment baseline characteristics and laboratory results [including: complete blood count (CBC), comprehensive metabolic panel (CMP), prothrombin time with international normalized ratio, HCV RNA, HCV GT, alpha fetoprotein, vitamin D, glycosylated hemoglobin (HgbA1C), human immunodeficiency virus (HIV), hepatitis B core antibody (anti-HBc), hepatitis B surface antigen (HBsAg), hepatitis A antibody total, IL-28b genotype, and pregnancy test [for women of childbearing age] were assessed. HBV DNA testing was done for those who were found to be anti-HBc positive. Those who were not immune or previously vaccinated for hepatitis A and B were offered and started on the appropriate vaccine series prior to treatment.

Liver fibrosis was assessed by either vibration controlled transient elastography (VCTE) using FibroScan[®], serum fibrosis test, or liver biopsy. A pre-treatment VCTE was performed on all patients who were treated through the ANTHC LDHP, except for the first 7 who had begun treatment prior to availability of VCTE at ANTHC. Fibrosis stage was assessed according to Metavir-equivalent scoring (F0 to F4). Median VCTE level ≥ 12 kPa was defined as cirrhosis.

A thorough health history was completed prior to treatment. This included presence or history of the following: any liver disease or cirrhosis; pulmonary disorders; cardiovascular disease; including deep vein thrombosis and pulmonary embolism; autoimmune disorders; organ transplant; cancer; current infection; high blood pressure; dyslipidemia; kidney disease; anemia; current TB treatment; diabetes Type 1 or 2; HIV; seizure disorder; and mental health conditions. A complete medication history, which included both prescription and over-the-counter supplements, was obtained to identify any potential interactions with sofosbuvir-based drugs. Participants' vaccine status for influenza, pneumonia, tetanus and Tdap, and shingles were reviewed and those who were not up-to-date on those vaccines were offered them prior to treatment.

The safety and tolerability of antiviral drug regimens were assessed by reviewing the answers on the baseline self-reported symptoms inventory completed prior to treatment and subsequent symptoms inventories which were completed monthly through the end of treatment, to assess for potential adverse effects related to HCV treatment. Symptoms included in the inventory were: feeling excessively tired (fatigue), flu-like illness, chills, fever, weakness, trouble sleeping, headache, hair loss, dry mouth, cough, shortness of breath, decreased appetite, nausea, vomiting, weight loss, heartburn or upset/sour stomach, muscle aches, joint aches, back pain, itching, rash, dizziness, irritability, depression or anxiety, changes in mood/mood swings, and feeling forgetful/problems concentrating. Patients were asked about any positive symptoms identified to determine if circumstances or other comorbidities were contributing to them.

Prior to treatment start, an HCV treatment agreement was signed by the patient which explained the treatment process, possible side effects, drug interactions, expected efficacy, and asked the patient to agree to the following:

- Not to drink alcohol or use recreational drugs during treatment.
- Report any serious medical conditions, including heart disease, high blood pressure, diabetes, high cholesterol, rheumatoid arthritis, drug addiction, or psychiatric condition.
- Commit to taking medications as prescribed and if unable to do so to contact provider.
- Protect self and others from hepatitis C by not sharing needles, drug works, razors, toothbrushes, or nail clippers, and cover cuts to prevent blood exposure.

When this study began there were enough unknowns about these newer hepatitis C medications that it was considered prudent to discourage use of alcohol or drugs not prescribed by a licensed medical provider while being treated. The ANTHC Medical Executive Committee endorsed the use of this agreement during the protocol review process. We explained to patients during recruitment that they would not be penalized if they broke the agreement. And if a patient identified as having a substance use disorder, referral to behavioral health was offered. There were 15 patients (3%) who refused to consent to the study. Anyone who refused to consent to the study was linked to standard treatment.

Labs obtained monthly during treatment and analyzed included: HCV RNA, CBC, CMP, HBV DNA (if HBsAg positive or if HBV DNA present in those who were anti-HBc positive prior to treatment), and pregnancy test on women of childbearing age.

Treatment completion or discontinuation of medications was documented. Treatment completion was defined as the patient having an end of treatment clinic visit or direct communication with the LDHP or primary care clinic staff verifying that all medication had been taken. Treatment efficacy as determined by sustained virologic response (SVR) 12 weeks after treatment completion was assessed using HCV RNA (COBAS(R) AmpliPrep /COBAS(R) TaqMan(R) HCV Test Kit (Roche Molecular Systems, Inc., Pleasanton, CA). CBC, hepatic function panel and AFP were drawn at SVR time point and VCTE was repeated to assess liver fibrosis at that time.

One year after treatment completion, VCTE was repeated to reassess liver fibrosis.

All patients whose pre-treatment fibrosis assessment (either by VCTE, serum fibrosis test, or liver biopsy) indicated advanced liver fibrosis (Metavir F3-F4 equivalent fibrosis) were instructed to continue to have right upper quadrant (RUQ) ultrasound along with AFP blood test every 6 months as surveillance for HCC.

Data analysis

For the outcome of DAA treatment success rate, we calculated SVR in an intention-to-treat analysis and a per-protocol analysis. The intention-to-treat analysis included all persons who started HCV treatment. The per-protocol analysis removed persons who discontinued treatment early, regardless of their virologic response and persons who were lost to follow-up with an unknown virologic response. We compared the SVR rate using a likelihood ratio χ^2 or Cochran-Armitage test of trend. The high SVR rates with an associated low sample size of treatment failures limited the building of multivariable logistic regression models. We used forward selection with log-binomial regression. After inclusion of the most significant univariate variable, no statistically significant multivariable models were found. We compared alanine aminotransferase (ALT), AFP and VCTE results before and after treatment using a normal or log-normal response and generalized estimating equations were used to account for repeated measurements. The prevalence of side effects reported on the symptoms inventory was compared between the start and end of treatment using generalized estimating equations logistic regression. We used the start of treatment as the start of follow-up and the date of HCC detection, death date, or Dec 1, 2019 as the end of follow-up for calculating HCC incidence following treatment. Exact *P*-values were reported when sample size necessitated. All analyses were run in SAS version 9.4 and a *P*-value < 0.05 was considered statistically significant.

Ethical considerations

This study was approved by the Alaska Area Institutional Review Board (protocol # 2012-06-021) and the ANTHC and Southcentral Foundation (SCF) Research Review Committees. Informed written consent for the study was obtained from all participants. ANTHC and SCF

Research Review Committees and CDC reviewed this manuscript. Dana Bruden and Brenna Simons, authors, are employed by the CDC. The findings and conclusions in this study are those of the authors and do not necessarily represent the official position of the CDC.

Results and discussion

Characteristics of study participants

Characteristics of patients at baseline are shown in [Table 2](#). The final data analysis occurred on 501 AN/AI persons who received *sofosbuvir*-based treatment from March 2014 to December 2018. Seventy-five percent of treatments were prescribed by ANTHC LDHP providers on the ANMC campus in Anchorage; ($n = 378$); 25% were prescribed by providers at other Alaska Tribal facilities.

For comparison, study participants were divided into three groups based on the treatment regimen: ledipasvir/sofosbuvir, sofosbuvir plus ribavirin, and sofosbuvir/velpatasvir. Sofosbuvir-based treatment type and duration of treatment were determined by HCV GT, and fibrosis status in accordance with AASLD/IDSA treatment guidance available at the time of treatment [27].

Median age of study participants was 54.3 years, ranging from 21.3 to 78.3. The majority of patients were GT-1a [327 (65%)]; male [272(54%)], and treatment naïve [474(95%)]. The mean body mass index (BMI) was 28.0; 122/417 (29%) patients had a BMI greater than 30. Advanced fibrosis occurred in 134/497 (27%) persons and 69/497 (14%) patients had cirrhosis (F4). HCV RNA greater than six million international units/ml was observed in 92/501 (18%) patients.

Of the 501 persons, 480 (96%) completed their treatment regimen. Twenty percent (93/460) of persons were anti-HBc positive prior to sofosbuvir-based treatment; with 4 of those having chronic hepatitis B (HBsAg positive). Four participants who reported ongoing injection drug use had achieved SVR and then had HCV RNA detected at a later time point, suggesting reinfection. Eight patients (2%) were HIV positive. There were no positive pregnancy tests during the study.

Therapeutic response for sofosbuvir-based treatment in AN/AI people

Sofosbuvir-based medication consisted of ledipasvir/sofosbuvir ($n = 348$), sofosbuvir/velpatasvir ($n = 94$), and sofosbuvir plus ribavirin ($n = 59$). The most frequent treatment length was 12 weeks (74%), followed by 8 weeks (22%), 24 weeks (3%), and 16 weeks (1%).

SVR was analyzed for both intention-to-treat and per-protocol groups in [Table 3](#).

First, we looked at SVR in the intention-to-treat analysis. Overall SVR rate for sofosbuvir-based treatment was 95.2% (477/501); for the patients treated at ANMC, SVR was 95.8% versus 93.5% at other Alaska locations. This difference was not statistically significant. Females did not differ in treatment success compared with males ($P = 0.09$). Patients who completed treatment had significantly higher treatment success compared to those who did not finish treatment ($P < 0.0001$). Those with cirrhosis responded as well to treatment as those without cirrhosis. Additionally, there were no significant differences in treatment success by age, HCV GT, IL-28b GT, anti-HBc positive status, or having undergone a previous HCV treatment.

We next looked at SVR per-protocol (removing those who discontinued treatment and persons lost to follow up following treatment completion). These exclusion criteria reduced the analysis cohort to 479 persons. Overall treatment success improved to 97.3% (466/479). SVR was significantly higher for patients treated at ANMC compared to other Alaska locations ($P = 0.02$). Fibrosis level at treatment start became significant to treatment success ($p < 0.01$) in the per-protocol analysis. Age, sex, HCV GT, and IL-28b status remained non-significant. Higher SVR rate of those without presence of cirrhosis was significant ($P = 0.002$) as compared

Table 2. Characteristics of 501 AN/AI persons treated for hepatitis C in Alaska using sofosbuvir-based DAA therapy, Alaska (treated March 2014– December 2018).

Characteristic	Level	All Persons % (n = 501)	Persons Treated at ANMC % (n = 378)
Treatment Location	ANMC	75% (378)	100% (378)
	Non-ANMC	25% (123)	
Completed Therapy		96% (482)	95% (360)
Previously treated		5% (27)	6% (22)
IL28b (n = 326)	CC	45% (145)	45% (120)
	CT	46% (151)	46% (124)
	TT	9% (30)	9% (25)
Known HIV Positive		2% (8)	1% (5)
Treatment Length	8 Weeks	22% (109)	22% (84)
	12 Weeks	74% (372)	74% (279)
	16 Weeks	1% (6)	1% (4)
	24 Weeks	3% (14)	3% (11)
Treatment Regimen	Sofosbuvir+Ribavirin	12% (59)	12% (45)
	Ledipasvir/Sofosbuvir	70% (348)	67% (252)
	Sofosbuvir/Velpatasvir	18% (94)	21% (81)
HCV GT	1a	65% (327)	64% (242)
	1b	10% (52)	10% (39)
	2	15% (75)	16% (59)
	3	9% (45)	10% (37)
	4, 6	0.4% (1 each)	0.3% (1 GT 6)
Female Gender		46% (229)	47% (177)
Characteristics at Start of Treatment			
Median Age (range)		54.3 Years (21.3, 78.3)	52.3 years (22.3, 72.7)
Mean BMI		28.0	28.1
% BMI ≥ 30		29% (122/417)	30% (106/356)
Advanced Fibrosis (F3-F4) or F4)		27% (134/497)	22% (84)
Cirrhosis (F4)		14% (69/497)	13% (49)
Median ALT (min, max) at Treatment Start ^b		52 (7, 612)	51 (7, 612)
HCV RNA ≥ 6 million ^a		18% (92)	20% (76/378)
Vitamin D < 30 iu/mL ^a		45% (185/415)	45% (153/341)
Vitamin D < 20 iu/mL ^a		15% (64/415)	15% (50/341)
Mean A1C % (min, max) ^b		5.6 (4.4, 11.6)	5.4 (4.4, 11.6)
Median AFP ^b		3.6 (0.6, 226.1)	3.4 (0.6, 226.1)
Median GFR (mL/min) ^b		94 (38, 257)	98 (38, 257)
Positive Anti-HBc ^b		20% (93/460)	19% (67/360)

^a–These labs were collected between 24 weeks prior to treatment start until one week after treatment start. The closest chronologically to the treatment start date was used in calculation of mean or median.

^b–At any time point prior to treatment.

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to those with compensated cirrhosis. Also, those who had not undergone previous HCV treatment had a significantly higher SVR rate ($P = 0.03$) compared to those who had been previously treated.

Eleven persons developed HCC after their treatment (range of 3 months to 3.7 years after treatment); all had F3 to F4 fibrosis prior to treatment. HCC incidence following DAA treatment was 6.37 cases per 1000 person-years of follow-up.

Table 3. Treatment success results among AN/AI (sustained virologic response at 12 weeks post treatment) by intention-to-treat and per-protocol analyses with 95% confidence intervals [CI], Alaska, treated March 2014– December 2018.

Category	Level	SVR Intention-to-treat	P-value for Difference	SVR Per-protocol ^a	P-value for Difference
Overall		95.2% [93.3, 97.1]		97.3% [95.8, 98.7]	
Sex	Female	96.9% [93.8, 98.8]	0.09	98.2% [95.4, 99.5]	0.26
	Male	93.8% [90.9, 96.6]		96.5% [94.3, 98.8]	
Age	< 40 years	93.3% [89.7, 98.7]	0.95	99.0% [94.3, 99.9]	0.18
	40–59 years	95.9% [93.6, 98.3]		97.3% [95.3, 99.3]	
	≥ 60 years	94.5% [90.6, 98.5]		96.0% [92.5, 99.4]	
Birth Cohort	Pre 1966	95.0% [92.6, 97.4]	0.75	96.4% [94.3, 98.5]	0.15
	After 1966	95.6% [92.6, 98.6]		98.8% [95.9, 99.9]	
Treatment Location	ANMC	95.8% [93.7, 97.8]	0.32	98.3% [96.4, 99.4]	0.02
	Rural	93.5% [89.1, 97.9]		94.2% [88.4, 97.6]	
Completed Treatment	Yes	97.9% [96.0, 99.1]	<0.0001	Not Applicable	
	No	54.6% [32.2, 75.6]		Not Applicable	
Treatment Regimen	Led/Sof ^b	96.8% [95.0, 98.7]	0.004 ^c	97.9% [96.4, 99.4] ^d	0.01 ^c
	Sof/Riba	86.4% [77.7, 95.2]		90.6% [82.7, 98.4]	
	Sof/Vel	94.6% [88.0, 98.3]		98.9% [94.0, 100.0]	
BMI ≥ 30	Yes	92.6% [88.0, 97.3]	0.13	94.0% [89.7, 98.3]	0.02
	No	96.3% [94.1, 98.4]		98.6% [96.4, 99.6]	
Steatosis (CAP > 248)	Yes	92.8% [88.7, 96.9]	0.09	94.6% [91.0, 98.2]	0.05
	No	97.0% [94.3, 99.6]		98.7% [99.5, 99.9]	
A1c ≥ 5.7	Yes	94.6% [86.7, 98.5]	0.76	97.2% [90.3, 99.7]	1.00
	No	95.5% [93.1, 97.9]		97.8% [96.0, 99.5]	
Hep B Core + ^e	Yes	93.6% [88.6, 98.5]	0.40	93.3% [88.2, 98.5]	0.08
	No	95.9% [93.9, 97.9]		98.3% [96.9, 99.7]	
Fibrosis Level	F0-F1	96.1% [93.9, 98.4]	0.13	99.3% [97.4, 99.9]	0.002 ^f
	F2	96.2% [89.2, 99.2]		97.4% [90.8, 99.7]	
	F3	92.3% [83.0, 97.5]		93.4% [84.1, 98.2]	
	F4	92.8% [83.9, 97.6]		92.7% [83.7, 97.6]	
HCV GT	1a	95.1% [92.7, 97.4]	0.14	97.4% [95.0, 98.9]	0.38
	1b	100.0% [93.2, 100.0]		100.0% [93.0, 100.0]	
	2	94.7% [86.9, 98.5]		95.9% [88.5, 99.1]	
	3	91.1% [78.8, 97.5]		95.1% [83.5, 99.4]	
HCV RNA Level	≥ 6 million	92.4% [87.0, 97.8]	0.28	95.4% [88.5, 98.7]	0.26
	< 6 million	95.8% [93.9, 97.8]		97.7% [96.2, 99.2]	
IL-28b	CC	97.9% [94.1, 99.6]	0.22	98.6% [95.0, 99.8]	0.15
	CT	94.0% [90.3, 97.8]		95.2% [91.7, 98.7]	
	TT	93.3% [77.9, 99.2]		100.0% [87.2, 100.0]	
Compensated Cirrhosis	Yes	92.8% [83.9, 97.6]	0.36	92.7% [83.7, 97.6]	0.03
	No	95.6% [93.6, 97.5]		98.0% [96.7, 99.4]	
Treatment Naive	Yes	95.6% [93.7, 97.4]	0.13	97.8% [96.4, 99.2]	0.03
	No	88.9% [70.8, 97.7]		88.5% [69.9, 97.6]	

^a–Persons Discontinuing Treatment Were Removed and Persons with Unknown SVR

^b–P-value for Ledsof 8-week (99.1%, 108/109) vs. Ledsof 12-week (95.8%, 229/239) treatment = 0.18

^c–P-value is for Led/Sof and Sof/Vel vs. Sof/Riba

^d–P-value for Ledsof 8-week (99.1%, 108/109) vs. Ledsof 12-week (97.4%, 221/227) treatment = 0.44

^e–all 4 persons who were positive for HBsAg responded with an SVR at 12 weeks

^f–P-value for F0-F1-F2 vs. F3-F4.

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There were four HCV re-infections (<1%) that occurred in participants who had achieved SVR. All four were found to have a different GT, and had known continued injection drug use. Having resolved hepatitis B infection, isolated anti-HBc positive, or chronic hepatitis B (HBsAg-positive) did not affect SVR rate in our AN/AI cohort. Also, there were no flares of hepatitis B (defined as elevated ALT >2 ULN and HBV DNA > 2,000 IU/mL in persons with previously inactive or resolved HBV) among those who were anti-HBc+ [28], including those with chronic hepatitis B during treatment. There was one death while on HCV treatment due to non-liver related cancer, and two deaths of unknown cause following HCV treatment completion but prior to SVR testing. One death occurred 1 month after treatment completion and the other occurred 13 months after completion.

Changes in treatment characteristics from pre to post treatment

We investigated changes in ALT, AFP, and VCTE fibrosis score pre to post treatment for those at ANMC only. We focused on the ALT and AFP as markers of inflammation and fibrosis progression as well as their associations with adverse outcome, hepatitis C flares and liver cancer, respectively. All characteristics explored were significant regardless of SVR (Table 4). Treatment success led to reduced AFP levels post treatment and significant reductions in fibrosis scores by VCTE 1–2 years after treatment.

Side effects

Changes in the prevalence of adverse effects, collected through the symptoms inventory, between week 0 and the end of treatment, were analyzed by treatment regimen from the patients treated at ANMC (Table 5). Persons who received sofosbuvir plus ribavirin experienced an increase in mood changes ($P = 0.040$), shortness of breath ($P = 0.003$), and dizziness ($P = 0.040$). Those who received ledipasvir/sofosbuvir reported only an increase in headache ($P = 0.004$) on treatment, and those who received sofosbuvir/velpatasvir did not show any statistically significant increases in symptoms during treatment. There was one person who discontinued treatment after one day taking sofosbuvir/velpatasvir because of urticaria. One person discontinued sofosbuvir plus ribavirin after hospitalization for non-ST segment elevation myocardial infarction secondary to coronary vasospasm.

Conversely, after SVR there was a reported significant decrease in joint pain by participants receiving any of the three regimens. Those who received sofosbuvir + ribavirin and ledipasvir/sofosbuvir reported a significant decrease in back pain. Those who received sofosbuvir/velpatasvir reported less depression ($P = 0.02$) and less decreased appetite ($P < 0.01$). Additionally, those who were treated with ledipasvir/sofosbuvir regimens reported significant decreases in trouble sleeping ($P = 0.020$), joint pain ($P = 0.001$), back pain ($P = 0.002$), and muscle pain ($P = 0.040$).

Discussion

In this sofosbuvir-based treatment study of AN/AI patients with HCV, overall SVR was achieved by 95.2% of participants. These SVR rates are comparable to rates found in other ethnic groups [24, 29]. There were no statistically significant differences in SVR rate by HCV GT, or IL-28b GT. Sofosbuvir-based HCV treatment regimens were effective and tolerated well by AN/AI persons.

The introduction of all-oral sofosbuvir therapeutic regimens for the treatment of chronic hepatitis C has led to remarkable improvement in SVR, providing therapeutic options to patients with contraindications to IFN-based regimens as well as those who either failed or were intolerant to IFN. However, despite the more convenient dosing schedules and shorter

Table 4. Changes in fibrosis markers among AN/AI pre and post treatment for persons^a treated with sofosbuvir-based DAAs at ANMC^b, Alaska, treated March 2014– December 2018.

Variable	Cohort	Pre Treatment ^c	Post Treatment ^d	P-value	Post Treatment 2 ^e
Median ALT ^f	Among All	51.0 (7, 612)	16.0 (4, 120)	< 0.0001	
		(n = 379)	(n = 334)		
	Success SVR	51.0 (7, 612)	16.0 (4, 120)	< 0.0001	
		(n = 352)	(n = 313)		
Median AFP ^g	Among All	3.4 (0.6, 226.1)	3.0 (0.9, 440.7)	< 0.0001	
		(n = 378)	(n = 283)		
	Success SVR	3.4 (0.6, 87.9)	3.0 (0.9, 440.7)	< 0.0001	
		(n = 351)	(n = 265)		
Median AFP (Among All)	F0-F1	3.0 (0.6, 14.1)	2.8 (1.0, 14.4)	0.0004	
		(n = 240)	(n = 177)		
	F2	3.5 (0.7, 22.5)	3.2 (0.9, 9.4)	0.008	
	F3-F4	6.3 (1.7, 226.1)	3.7 (1.6, 440.7)	<0.0001	
		(n = 84)	(n = 67)		
	F2	3.5 (0.7, 22.5)	3.2 (0.9, 9.4)	0.005	
Median AFP (Among those who achieved SVR)	F0-F1	3.0 (0.6, 14.1)	2.7 (1.0, 14.4)	<0.0001	
		(n = 223)	(n = 167)		
	F2	3.5 (0.7, 22.5)	3.2 (0.9, 9.4)	0.005	
	F3-F4	6.3 (1.7, 87.9)	3.6 (1.6, 440.7)	<0.0001	
		(n = 76)	(n = 60)		
	F2	3.5 (0.7, 22.5)	3.2 (0.9, 9.4)	0.005	
VCTE ^h	Among All	5.7 (2.3, 46.4)	5.1 (2.3, 75.0)	<0.0001	
		(n = 308)	(n = 291)		
	Success SVR	5.8 (2.3, 46.4)	5.1 (2.3, 75.0)	0.02	5.0 (2.7, 48)
		(n = 289)	(n = 283)		
VCTE (Among All)	F0-F1	5.1 (2.3, 10.4)	4.6 (2.3, 21.3)	0.03	
		(n = 200)	(n = 180)		
	F2	7.6 (3.0, 12.5)	5.3 (2.7, 12.1)	<0.0001	
	F3-F4	11.9 (4.5, 46.4)	9.4 (3.3, 75.0)	<0.0001	
		(n = 59)	(n = 66)		
	F2	7.6 (3.0, 12.5)	5.3 (2.7, 12.1)	<0.0001	
VCTE (Among those who achieved SVR)	F0-F1	5.1 (2.3, 7.9)	4.6 (2.3, 21.3)	0.03	4.6 (2.7, 19.0)
		(n = 186)	(n = 175)		(n = 125)
	F2	7.6 (3.0, 12.5)	5.3 (2.7, 12.1)	<0.0001	4.6 (2.9, 9.5)
	F3-F4	12.1 (4.5, 46.4)	8.8 (3.3, 75.0)	<0.0001	7.4 (4.1, 48.0)
		(n = 56)	(n = 63)		(n = 57)

^a—n = 378

^b—Alaska Native Medical Center

^c—from 6 weeks prior to treatment start to 1 week after treatment start

^d—from 12–36 weeks after treatment stopped

^e—from 1 years to < 2 years post therapy

^f—ALT = alanine aminotransferase

^g—AFP = alpha fetoprotein

^h—VCTE = vibration controlled transient elastography.

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Table 5. Symptoms experienced according to hepatitis C treatment regimen among an Alaska Native/American Indian cohort^a, treated March 2014-December 2018.

Side Effect ^b	Treatment Week	Drug Regimen		
		Sofosbuvir/Ribavirin	Ledipasvir/Sofosbuvir	Sofosbuvir/Velpatasvir
		(n = 45)	(n = 252)	(n = 81)
Tired	0	41% (18/44)	35% (87/246)	51% (37/73)
	End of Treatment	41% (15/37)	33% (73/221)	43% (30/69)
<i>P</i> -value		0.95	0.54	0.37
Headache	0	16% (7/44)	26% (64/246)	25% (18/73)
	End of Treatment	22% (8/37)	36% (79/221)	25% (17/69)
<i>P</i> -value		0.24	0.004 ↑	0.86
Trouble Sleeping	0	36% (16/44)	43% (106/246)	42% (31/73)
	End of Treatment	49% (18/37)	35% (78/221)	38% (26/69)
<i>P</i> -value		0.38	0.02 ↓	0.58
Joint Pain	0	52% (23/44)	44% (109/246)	51% (37/73)
	End of Treatment	27% (10/37)	32% (70/221)	38% (26/69)
<i>P</i> -value		0.009 ↓	0.001 ↓	0.04 ↓
Back Pain	0	45% (20/27)	44% (107/246)	55% (40/73)
	End of Treatment	22% (8/37)	33% (72/221)	42% (29/69)
<i>P</i> -value		0.01 ↓	0.002 ↓	0.06
Muscle Pain	0	32% (14/44)	39% (96/246)	42% (31/73)
	End of Treatment	24% (9/37)	31% (69/221)	33% (23/69)
<i>P</i> -value		0.27	0.04 ↓	0.21
Forgetful	0	23% (10/44)	31% (76/246)	32% (23/73)
	End of Treatment	32% (12/37)	25% (56/221)	28% (19/69)
<i>P</i> -value		0.30	0.12	0.64
Dry Mouth	0	18% (8/44)	24% (59/246)	15% (11/73)
	End of Treatment	24% (9/37)	24% (54/221)	22% (15/69)
<i>P</i> -value		0.39	0.76	0.14
Weakness	0	9% (4/44)	18% (45/246)	30% (22/73)
	End of Treatment	24% (9/37)	21% (46/221)	26% (18/69)
<i>P</i> -value		0.08	0.36	0.64
Irritability	0	16% (7/44)	16% (39/246)	21% (15/73)
	End of Treatment	32% (12/37)	15% (34/221)	16% (11/69)
<i>P</i> -value		0.09	0.86	0.44
Depression	0	11% (5/44)	25% (62/246)	34% (25/73)
	End of Treatment	24% (9/37)	21% (46/221)	22% (15/69)
<i>P</i> -value		0.06	0.23	0.02 ↓
Itching	0	14% (6/44)	15% (38/246)	19% (14/73)
	End of Treatment	27% (10/37)	14% (30/221)	19% (13/69)
<i>P</i> -value		0.10	0.32	0.98
Changes in Mood	0	14% (6/44)	17% (42/246)	23% (17/73)
	End of Treatment	30% (11/37)	17% (38/221)	16% (11/69)
<i>P</i> -value		0.04 ↑	0.92	0.27
Heartburn	0	11% (5/44)	21% (52/246)	26% (19/73)
	End of Treatment	19% (7/37)	19% (42/221)	23% (16/69)
<i>P</i> -value		0.34	0.43	0.60
Shortness of Breath	0	7% (4/44)	14% (34/246)	30% (22/73)
	End of Treatment	35% (13/37)	14% (30/221)	22% (15/69)

(Continued)

Table 5. (Continued)

Side Effect ^b	Treatment Week	Drug Regimen		
		Sofosbuvir/Ribavirin	Ledipasvir/Sofosbuvir	Sofosbuvir/Velpatasvir
		(n = 45)	(n = 252)	(n = 81)
<i>P</i> -value		0.003 ↑	0.95	0.15
Nausea	0	5% (2/44)	11% (26/246)	22% (16/73)
	End of Treatment	8% (3/37)	16% (35/221)	28% (19/69)
<i>P</i> -value		0.48	0.05	0.41
Blurred Vision	0	16% (7/44)	18% (44/246)	21% (15/73)
	End of Treatment	19% (7/37)	15% (34/221)	15% (10/69)
<i>P</i> -value		0.71	0.42	0.36
Decreased Appetite	0	9% (4/44)	13% (32/246)	25% (18/73)
	End of Treatment	14% (5/37)	13% (29/221)	9% (6/69)
<i>P</i> -value		0.53	0.97	0.009 ↓
Diarrhea	0	5% (2/44)	8% (19/246)	14% (10/73)
	End of Treatment	14% (5/37)	11% (24/221)	13% (9/69)
<i>P</i> -value		0.08	0.21	0.95
Cough	0	9% (4/44)	15% (36/246)	21% (15/73)
	End of Treatment	16% (6/37)	12% (27/221)	20% (14/69)
<i>P</i> -value		0.32	0.43	0.95
Chills	0	2% (1/44)	9% (23/246)	15% (11/73)
	End of Treatment	16% (6/37)	11% (25/221)	23% (16/69)
<i>P</i> -value		0.06	0.46	0.17
Dizziness	0	2% (1/44)	9% (23/246)	22% (16/73)
	End of Treatment	19% (7/37)	10% (22/221)	12% (8/69)
<i>P</i> -value		0.04 ↑	0.86	0.09
Flu-Like Symptoms	0	9% (4/44)	7% (16/246)	11% (8/73)
	End of Treatment	5% (2/37)	11% (25/221)	17% (12/69)
<i>P</i> -value		0.43	0.05	0.21
Rash	0	11% (5/44)	8% (20/246)	12% (9/73)
	End of Treatment	15% (6/37)	7% (16/221)	10% (7/69)
<i>P</i> -value		0.44	0.65	0.83
Hair Loss	0	5% (2/44)	6% (15/246)	12% (9/73)
	End of Treatment	8% (3/37)	10% (23/221)	17% (12/69)
<i>P</i> -value		0.49	0.07	0.33
Vomiting	0	5% (2/44)	4% (10/246)	7% (5/73)
	End of Treatment	3% (1/37)	3% (7/221)	6% (4/69)
<i>P</i> -value		0.68	0.48	0.77
Anemia	0	0% (0/44)	0% (0/246)	1% (1/73)
	End of Treatment	3% (1/37)	3% (6/221)	0% (0/69)
<i>P</i> -value		Not tested	Not tested	Not tested
Fever	0	0% (0/44)	3% (8/246)	7% (5/73)
	End of Treatment	0% (0/37)	5% (12/221)	7% (5/69)
<i>P</i> -value		Not tested	0.24	0.93

^a—statistically significant *P*-value change shown in bold with arrow to indicate increase (↑) or decrease (↓) in symptom

^b—data collected on 33 symptoms.

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durations of treatment and high cure rates, a small percentage of patients experience treatment failure. The SVR results of our study are in line with earlier studies reporting SVR rates between 87% and 99% [29–34]. Furthermore, 92.8% of patients with compensated cirrhosis achieved SVR. The SVR rate for cirrhosis patients achieved in our study is similar to those reported in phase 2 and 3 clinical trials [30–32].

We assume the high SVR rate of 97.3% in those who completed the study per-protocol was achieved due to high adherence rate and close monitoring and follow-up by experienced nurses and health care providers.

In our study the decreases in non-invasive serological markers (ALT, AFP) and VCTE fibrosis scores suggest a significant regression of inflammation and liver fibrosis in patients at SVR12 as compared to baseline. Several studies have shown the same results; however, the effect was more pronounced in patients with baseline VCTE scores suggesting advanced stages of fibrosis and cirrhosis [35, 36]. However, the findings of decreases in liver stiffness scores might be influenced by inflammation, resulting in lower kPa measurements after SVR, which has been previously found in patients with chronic hepatitis [37].

Hepatitis due to reactivation of HBV infection during treatment with DAAs for chronic HCV infection has been reported in patients who were anti-HBc+ prior to treatment. In general, an HBV flare is defined as elevated ALT and HBV DNA > 2,000 IU/mL in persons with previously inactive or resolved HBV infection. Findings from Loggi et al. [38] on 44 subjects who received DAA treatment for HCV infection, found no reactivation in those with past HBV infection (anti-HBc+ only). They also found that two persons who were HBsAg-positive experienced a flare of HBV infection, followed by HBsAg loss. Another study showed that hepatitis B reactivation was a rare event in anti-HBc+/HBsAg-negative patients treated with DAA therapy [34]. In our study there were a large number of anti-HBc+ patients (93). Eighty nine of these patients were anti-HBc+/HBsAg-negative whom we assume were infected with hepatitis B and recovered shortly after, and 4 patients were HBsAg-positive, having chronic hepatitis B coinfection. None of these 93 patients experienced flares of HBV during or immediately following treatment. This finding adds support to the body of knowledge showing hepatitis B flares, among those chronically infected and reactivation among those with resolved infection, as a result of HCV treatment, is rare.

HCV reinfection following successful treatment can compromise treatment outcomes. In our study population, we observed less than 1 percent reinfection rate due to ongoing drug use in those who achieved SVR during the span of the study follow up period. A recent meta-analysis showed an overall rate of HCV reinfection of 5.9/100 person-years (95% CI 4.1–8.5) among people with recent drug use (injecting or non-injecting), and 6.2/100 person-years (95% CI 4.3–9.0) among people recently injecting drugs [39].

Ideas about treatment restrictions for alcohol and drug use have evolved across the country as more knowledge has been gained about the safe use of DAAs in the setting of substance use disorders [40, 41]. It is important to note that following that trend, and to minimize explicit and implicit barriers to treatment access, we no longer ask patients to agree not to use drugs or alcohol during treatment.

In our study none of the participants experienced serious adverse effects. The symptoms that increased in frequency were: headache for *ledipasvir/sofosbuvir*, and changes in mood, shortness of breath, and dizziness on *sofosbuvir* plus *ribavirin*, which is likely due to ribavirin. That is in line with previous studies [30, 42, 43]. Mizokami et al [44] data shows that the most common adverse effects on sofosbuvir-based treatment are nasopharyngitis, anemia, headache and malaise. Difference in the results may be partially explained by the differences in inherent metabolic pathways and different drug-drug interactions.

The SVR rate was higher in patients treated per protocol at ANMC vs. rural settings. This could be due to LDHP clinical staff having more experience keeping in contact with patients on HCV treatment than those treated in rural setting. Also, getting medications to rural settings in Alaska can be more difficult which can cause delays or gaps in treatment. From lessons learned in this study, we recommend getting information on multiple ways to contact patients at the start of treatment. We also encourage clinical staff to check in with patients who might get lost to follow up during treatment via phone call or text on a regular basis. We provided a medication card for patients to keep in their wallet that explained what HCV medication(s) they were taking and provided contact information for the LDHP. Patients were instructed to show this card to the person whose care they were entrusted to, if hospitalized or jailed, to ensure linkage to continued care and treatment. We learned that it is important to ensure that prescription renewals are picked up well in advance of a patient running out of medication. More recently, we have begun encouraging writing prescription for the full course of HCV treatment, when payer source allows.

Our study adds to the body of evidence regarding successful hepatitis C treatment among racial minorities, specifically AN/AI people. It is the largest study to date of American Indian or Alaska Native persons with hepatitis C treated with DAAs [25]. Given the small number of eligible patients who declined participation in the study, we believe our results, in terms of both compliance and treatment success, are generalizable to other AN/AI patients who are connected to health care and interested in being treated for hepatitis C.

Limitations of our study are that the cohort includes only AN/AI persons, therefore our findings may not apply to other racial/ethnic groups. However, this cohort was described previously and found to closely represent the US population infected with HCV in terms of HCV GT distribution and risk factors for infection [15]. Also, we recognize limitations of our findings outside of a connected Tribal healthcare system.

Treatment of HCV infection does not only benefit those infected but also reduces the burden of hepatitis C at the population level [2]. Regardless of stage of liver disease, coinfection, complications there is a survival benefit of SVR [2]. Cure of HCV infection has a long term impact on the economic burden of disease [45]. Complications of HCV infection such as liver cirrhosis, HCC and transplantation are associated with high medical cost and use of healthcare resources [46]. From a public health perspective, the “treatment as prevention” model as undertaken by ANTHC LDHP is of great benefit. It may reduce the prevalence of HCV infection in the population in the long-term, leading to a lower transmission rate and incidence of disease. To achieve 2030 targets of a 90% reduction in new cases of HCV infection and a 65% reduction in liver-related death, a new capacity for screening and treatment should be built. Hepatitis C needs to become a disease of high priority in both clinical and public health settings.

Conclusion

Our treatment study with sofosbuvir-based regimens was effective for a broad range of AN/AI patients with HCV GT 1, 2, 3, 4, or 6 infection. The treatment was also effective among patients with cirrhosis. Our findings regarding AEs and SVR rates add to the body of knowledge that sofosbuvir-based DAAs are safe and efficacious for AN/AI People. These real-world findings, in a population not included in pre-licensure clinical trials, suggest that HCV treatment for AN/AI persons should lead to a long-term decrease in liver disease progression and prevention of the development of HCC and reduction in disparities of HCV liver disease for AN/AI People.

To date, over 1100 AN/AI persons in Alaska have been treated through the ATHS and cured of hepatitis C with DAA therapy. Our treatment structure has evolved over time as

information about safety and efficacy of these DAAs has grown, and so we have scaled back on required labs and follow up during treatment that were written into this study while maintaining high SVR rates. Currently, there remains 1040 known AN/AI persons in Alaska with untreated hepatitis C, including approximately 180 AN/AI persons living in over 100 isolated communities without primary care providers and not connected to the road system. Moving forward, the use of telemedicine and novel ways to test and treat HCV in rural communities are being explored so that all AN/AI people can access antiviral treatment, disparities in liver disease outcomes can lessen, and the overarching goal of HCV elimination can be met in the AN/AI population.

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