Background

The availability and effectiveness of direct-acting antiviral (DAA) medications has radically changed the assessment and consideration of substance use in HCV treatment decisions. Recommendations issued by the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America (AASLD-IDSA) HCV Guidance state that in the modern DAA treatment era recent or active injection-drug use should not be considered a contraindication to HCV treatment and requirements for pretreatment screening for illicit drug or alcohol use should be discontinued. The general approach to considering initiation of treatment of HCV for individuals with a prior history of substance use, including injecting drugs, should be the same as in patients with no history of drug use. Nevertheless, for persons with chronic HCV infection, substance use, either past or present, which encompasses the use of opioids, amphetamines, cannabis, cocaine, alcohol, and other drugs, may still be relevant to the individual’s overall health and medication access. Substance use disorders are common in the United States, with 2015 data indicating that among persons 18 years of age or older, approximately 10% had used illicit drugs in the past month and approximately 51% had used illicit drugs in their lifetime. The following discussion will address the potential impact of substance use on HCV disease and HCV treatment.
Impact of Substance Use on HCV Treatment Outcomes

Potential Impact of Substance Use on Adherence

Earlier studies that examined adherence with interferon-based therapy in persons who inject drugs (PWID) found a modest decrease in adherence among persons with active injection drug use compared to others without active substance use.[3] In one review that included adherence data from 6 studies, the overall rate of nonadherence with interferon-based therapy was 6.8% among PWID with HCV treatment, compared with 4.9% of patients without drug use.[3] Multiple studies that have enrolled persons with active or recent injection drug use have shown excellent adherence with DAA therapy (Figure 1).[4,5,6] Persons with opioid use disorder who receive opioid agonist maintenance therapy (e.g. methadone, buprenorphine, or buprenorphine-naloxone) during HCV treatment have excellent rates of adherence, treatment completion, and sustained virologic response (SVR) rates, all comparable to results of other study participants.[7,8] In a large study that examined the impact of alcohol use on treatment outcomes with interferon-based therapy, recent alcohol use was associated with a slightly higher treatment discontinuation rate and a slightly lower SVR rate; past alcohol use did not impact these outcomes.[9] A separate study investigated different levels of alcohol intake and the impact on interferon-based therapies and found that low-moderate alcohol consumption did not impact SVR rates, but alcohol intake of 24 grams daily or higher reduced SVR rates. There are insufficient data related to the impact of past or recent alcohol use on outcomes with DAA therapy. One study examined the impact of past or active methamphetamine use in persons with chronic HCV treated with interferon-based regimens and methamphetamine use did not appear to significantly impact treatment completion or SVR rates. There are no published studies on the impact of methamphetamine use on DAA therapy.[10]

Duration of Abstinence to Maximize Treatment Outcome

Although some payers require 6 months or more of abstinence prior to HCV treatment, studies of both injection drug use and alcohol use have found no impact of duration of abstinence on likelihood of SVR.[3] There is no medical reason to ensure any duration of abstinence prior to HCV treatment. Current AASLD-IDSA Hepatitis C guidance recommendations do not consider substance use a contraindication to HCV treatment.[1] Institutional and provider-level stigma related to drug use can be a barrier for a client to initiate HCV treatment and this should be addressed with careful attention through the patient-provider relationship.

Impact of Treating People with Active Drug Use on HCV Transmission

Mathematical modeling, even assuming a reinfection rate equal to initial infection rates, has demonstrated that HCV treatment among persons with active injection drug use would result in a significant reduction in HCV transmission.[11,12,13,14] Several recent studies utilizing mathematical modeling based on DAA regimens concluded that scaling up HCV treatment in PWIDs would have a major impact in reducing HCV incidence and prevalence in this patient population, even more so in the setting of robust access to sterile injection equipment and opioid agonist maintenance services.[13] Further, scaling up and widespread treatment of HCV in PWID as a prevention tool, akin to treating HIV to reduce community viral load, has become a more realistic goal with the short-course, well-tolerated, interferon-free regimens.

Impact of Comorbidities in Persons with Substance Use Disorder

In clinical practice, treating persons with an active substance use disorder may be complicated by coexisting social problems and barriers erected by payers, but clinical experience suggests that, with appropriate infrastructure and patient support including the treatment of substance use disorders, HCV treatment is feasible in this population.[15,16,17,18,19] Examples of patient support include directly-observed therapy and related approaches, patient navigation, and group treatment models,
particularly in substance use disorder treatment settings.

HCV Treatment Outcomes with Interferon-Based Therapy in PWID

Treatment success rates with peginterferon and ribavirin have historically been comparable among current and former PWID, with the exception that frequent drug use during treatment was associated with lower SVR rates than drug abstinence or occasional drug use during treatment (Figure 2).\textsuperscript{[17,20,21]} In a meta-analysis, investigators evaluated HCV treatment outcomes in studies that included approximately 50% of participants with active injection drug use during the HCV treatment; all studies in this meta-analysis were conducted prior to DAA-based therapy.\textsuperscript{[22]} Overall, they concluded that persons with active injection drug use had SVR rates similar to reported rates among among persons who did not inject drugs (when receiving HCV treatment outside of a clinical trials setting).\textsuperscript{[22]} In a recent retrospective analysis from the University of California at San Diego,\textsuperscript{[23]} the HCV treatment SVR rates were evaluated across three different HCV treatment eras in persons coinfected with HIV who were seen in a clinic where active barriers to care, including drug or alcohol use were common.\textsuperscript{[23]} The SVR rates markedly increased in the DAA treatment era in this patient population (Figure 3).\textsuperscript{[23]}

HCV Treatment Outcomes with DAA Therapy in PWID

Despite the extensive data that have been generated with DAA-based therapies, relatively little data exists with the use of DAs in patients with active injection drug use. The following summarizes several key studies that have analyzed HCV treatment responses with DAA-based therapy in persons who inject drugs or who have previously injected drugs and were receiving opioid agonist therapy. Multiple studies clearly show that use of DAA-based therapy in persons with past or current injection drug use results in high SVR rates, comparable to those seen in persons who do not use drugs.\textsuperscript{[6]}

- **Elbasvir-Grazoprevir (C-EDGE CO-STAR):** In this phase 3, multinational study (C-EDGE CO-STAR), investigators evaluated HCV treatment with elbasvir-grazoprevir in 301 PWID who had also been receiving opioid agonist therapy (e.g. methadone, buprenorphine, or buprenorphine-naloxone maintenance) for at least 3 months prior to enrollment.\textsuperscript{[4]} Participants with chronic HCV genotype 1, 4, or 6 were randomized to immediately receive a 12-week course of elbasvir-grazoprevir (immediate treatment group) or to receive the 12-week course of elbasvir-grazoprevir after a 16-week delay (deferred treatment group). On day 1 of the study, 58% of the subjects had a positive urine drug screen (excluding opiate agonist therapy). Overall, when excluding participants who discontinued for non-treatment reasons, 91.5% in the immediate treatment group and 89.5% in the deferred treatment group achieved an SVR12; the treatment responses were excellent regardless of cirrhosis status and baseline drug screening results (Figure 4).\textsuperscript{[4]}

- **Ledipasvir-Sofosbuvir (ION Trials):** In the ION trials, participants with chronic HCV genotype 1 infection received 8, 12, or 24 weeks of ledipasvir-sofosbuvir.\textsuperscript{[24]} Investigators performed a pooled data analysis to compare HCV treatment response in participants receiving opioid substitution therapy during treatment (n = 70) with participants not receiving opioid substitution therapy (n = 1882).\textsuperscript{[24]} The two groups had similar treatment completion, adherence, and SVR12 rates (Figure 5).\textsuperscript{[24]} Among those receiving opioid substitution therapy, 66 (94%) of 71 achieved an SVR12.\textsuperscript{[24]}

- **Sofosbuvir-Based Treatment in Phase 3 Trials:** In a pooled analysis of data from phase 3 trials using sofosbuvir-based regimens, investigators compared HCV treatment responses in participants receiving opioid substitution therapy during treatment (n = 194) with participants not receiving opioid substitution therapy (n = 4549).\textsuperscript{[8]} There were no significant differences in SVR12 rates (94% in those receiving opioid substitution therapy versus 97% for those not receiving opioid substitution therapy).\textsuperscript{[8]}

- **Sofosbuvir-Velpatasvir (SIMPLIFY):** In this single-arm, open label, phase 4 study, 103 participants with chronic HCV infection genotype 1-6 and recent (within 6 months) injection drug use were treated with a 12-week course of sofosbuvir-velpatasvir.\textsuperscript{[3]} During the
treatment course, 61 (59%) of the participants were receiving opioid substitution therapy and 76 (74%) had used injection drugs in the month prior to starting treatment.[5] A total of 100 (97%) of the 103 participants completed treatment; 2 were lost to follow-up and one person died from an accidental overdose. Overall, 97 (94%) of participants achieved an SVR12.[5]

- **Sofosbuvir-Velpatasvir (ASTRAL Trials):** In a subset analysis of the phase 3 ASTRAL trials, investigators compared treatment response to sofosbuvir-velpatasvir in persons receiving opioid substitution therapy during treatment (n = 51) compared with those where they were not receiving opioid substitution therapy (n = 984).[7] Receipt of opioid substitution therapy did not impact treatment responses—96% of participants receiving opioid substitution therapy achieved an SVR12.[7]
**Opioid Use**

**Impact on Natural History of HCV**

Opioid use by injection is a major driver of HCV transmission, but opioid use itself, either orally or by injection, does not appear to speed progression of liver disease in persons with chronic HCV.\(^{25}\) Opioid analgesic use disorder is also a risk factor for HCV acquisition and transmission, particularly as some users transition from oral ingestion of prescribed opioids to illicit opioids, and potentially to higher risk modes of administration, such as injection.\(^{26,27}\)

**Pretreatment Requirements**

The AASLD-IDSA Hepatitis C guidance does not have a requirement for abstinence from opioids prior to HCV treatment.\(^{1}\) Indeed, active injection drug use in an individual with chronic HCV is considered by many to be a direct indication for HCV treatment, due to the potential benefit of reducing secondary HCV transmission.\(^{28,29}\) In contrast to these expert recommendations, some payers may require abstinence from non-prescribed opioids. There are three FDA-approved treatments for opioid use disorder – buprenorphine, methadone, and extended-release naltrexone. While methadone access is limited to designated Outpatient Treatment Programs, the other medications can be prescribed in the context of routine medical care.

**Management Strategies**

For persons with a past or current history of opioid use disorder, treatment of HCV infection would ideally be performed in a multidisciplinary setting whereby HCV treatment and opioid use disorder can be addressed, as well as other comorbidities that may exist.\(^{1}\) Multiple treatment options exist for opioid use. Agonist maintenance therapy is the most effective known treatment and has been shown to reduce the risk of new HCV infection.\(^{30}\) Data from interferon-based regimens demonstrate that patients receiving methadone, buprenorphine, or buprenorphine-naloxone for opioid agonist therapy respond to HCV treatment similar to populations not using drugs.\(^{31,32,33}\) Injectable extended-release naltrexone is also approved for opioid dependence, although access can be challenging and uptake can be limited. There are no known clinically significant interactions between opioid agonist therapies or naltrexone and currently approved DAA medications.\(^{34,35}\) A detailed discussion of opioid agonist therapy is beyond the scope of this topic review.

**Potential Reinfection with HCV among Persons who Inject Drugs**

Multiple other studies have shown significant risk of HCV reinfection in persons cured with HCV therapy. Thus, it is essential that persons with past or active injection drug use be counseled that they can become reinfected with HCV after achieving an SVR; this risk is significant in persons who inject drugs and it also can occur through sexual contact, particularly among men who have sex with men. In one study that clearly evaluated reinfection among treated PWIDs, the reinfection rate for those reporting ongoing injection after SVR was 5.3 per 100 person-years, suggesting a small ongoing risk comparable to that reported in one meta-analysis of late relapse or reinfection.\(^{36}\) It is important that programs for HCV treatment provide access to counseling for safe injection practices and opioid agonist therapy. Although unstudied, detailed guidance on safer injection techniques may mitigate this risk (i.e. ensuring a source of sterile syringes and other injection equipment, as well as reviewing possible sources of HCV transmission such as cottons, cookers, water, alcohol pads, or any syringes used to divide, prepare, or inject drugs).\(^{37}\)
Stimulant Use

Impact on HCV

Injection of cocaine or methamphetamine is another major driver of HCV transmission.[38,39,40] Other routes of administration of stimulants, such as intranasal, may also be associated with HCV transmission.[41] In addition, prolonged stimulant use may result in cardiac and cerebrovascular toxicity.

Pretreatment Requirements

There is no requirement for abstinence from stimulant use prior to HCV treatment. However, some payers may require abstinence from methamphetamine prior to starting treatment.

Management Strategies

Stimulant use is often more intermittent than opioid or alcohol use but can also be associated with periods of poor adherence to medical care. Pharmacologic options are limited, with multiple current trials underway for both methamphetamine and cocaine dependence.[42] In a double-blind, placebo-controlled, randomized trial conducted from 2012 to 2015, a 12-week course of extended-release naltrexone did not appear to reduce amphetamine use among dependent persons.[43] In a similar randomized, controlled trial, a 12-week course of aripiprazole, when given over a 12-week period, did not significantly reduce methamphetamine use.[44] Mirtazapine and possibly bupropion or modafinil have demonstrated some efficacy for reducing methamphetamine use among dependent persons, but there is no current standard of therapy for methamphetamine dependence at this time.[45,46,47]
Alcohol Consumption

Impact on Liver Fibrosis in Patients with Chronic HCV

Several studies have shown that heavy alcohol consumption (at least 60 grams/day in men and 40 grams/day in women) accelerates the progression of HCV-related hepatic fibrosis (Figure 6).[48,49] A typical alcohol drink (12 ounces of beer, 5 ounces of wine, and 1.5 ounces of whiskey) contains 12 grams of alcohol. An estimated one-third of patients with chronic HCV infection have cirrhosis attributable to heavy alcohol consumption.[50] In a study in Alaska, investigators compared outcomes in persons who recovered from HCV with those who had chronic HCV and found heavy alcohol use (at least 50 grams of alcohol daily) was associated with the highest incidence of end-stage liver disease, regardless of whether the individual had recovered from HCV or had chronic HCV infection.[51] In addition, separate studies have shown that progression of liver disease may continue among heavy alcohol users even if SVR is achieved with treatment of HCV. Taken together, the available data suggest reducing alcohol use is critical to liver health. The effects of low or moderate alcohol consumption on liver health are not well characterized for persons with chronic HCV infection.

Pretreatment Requirements

Although abstinence from alcohol is strongly encouraged for patients with chronic HCV infection, a requirement for abstinence from alcohol prior to HCV DAA treatment is no longer recommended.[1] Some payers may still require abstinence.

HCV Treatment Outcomes Among Persons With Alcohol Use

The literature is mixed on whether alcohol use impacts treatment outcomes. Among a privately insured cohort, pretreatment alcohol consumption patterns were unrelated to SVR attainment or HCV relapse after interferon-based treatment.[52] A Swiss retrospective study also found no difference in SVR among 554 patients stratified by alcohol use.[53] In contrast, some studies suggest that active or heavy alcohol use during treatment with peginterferon plus ribavirin diminishes treatment responses.[9,19,54] In one French prospective study, investigators enrolled 73 patients with chronic hepatitis C who were treated with peginterferon and ribavirin and had varying degrees of alcohol consumption: abstinence, low-risk consumption, and excessive consumption.[19] Abstinence referred to patients off alcohol during the entire treatment period. Low-risk consumption was defined as weekly consumption of no more than 21 standard drinks (10 g of pure ethanol) for men and no more than 14 drinks for women, and no more than 4 by drinking occasion. Excessive consumption was defined as drinking more than the limits defined for low-risk consumption on at least two occasions during the treatment period. Overall, patients with excessive alcohol use had lower SVR rates than those who were abstinent or had low-risk ingestion (Figure 7).[19] There are insufficient data to determine how alcohol consumption impacts DAA outcomes.

Management Strategies

Although abstinence from alcohol prior to HCV DAA treatment is no longer required, efforts should be made to ensure that ongoing alcohol use does not interfere with adherence or medical follow-up. Alcohol consumption is discouraged in patients with chronic HCV infection due to the hepatotoxic effects of alcohol. Multiple pharmacologic agents are available for alcohol use disorder, including naltrexone, acamprosate, and topiramate.[55] Among these, the most promising results have been seen with naltrexone given as a monthly injection. Brief counseling on alcohol has also shown reductions in use among patients with HCV infection. A multidisciplinary approach, involving personalized addiction care and case management, may provide further benefit in managing alcohol dependence.[19] One study reported reduced alcohol use following treatment with peginterferon-based regimens for HCV infection.[56] It is unclear whether reduced alcohol intake would occur after
treatment with DAA-based therapy.
Cannabis

There is mixed evidence regarding cannabis use and HCV-related hepatic fibrosis progression.\cite{57,58,59} Two separate longitudinal cohort studies found no association between cannabis use and progression of liver fibrosis among patients coinfected with HCV and HIV.\cite{57,60} In addition, one study found a positive association between cannabis use and good adherence with HCV treatment.\cite{61} Although individuals living with HCV are generally advised to abstain from regular cannabis use, ongoing cannabis use is not considered a contraindication for initiating HCV therapy.
Summary Points

- Active substance use or use disorder is not a contraindication to HCV treatment.

- Treatment of HCV in persons with active injection drug use may have public health benefits in terms of reduced secondary HCV transmission.

- It is important to talk to patients about their substance use not insofar as to determine treatment eligibility but to understand how best to support them through treatment and prevent reinfection.

- Treatment of persons actively injecting drugs may have public health benefits in terms of reduced secondary transmission.

- Patients should be aware that heavy use of alcohol may reduce the benefits of HCV treatment.

- Therapeutic approaches to substance use disorders are generally more effective when including a pharmacologic agent.

- Care should be taken to ensure that PWIDs are aware of specific drug use techniques to avoid reinfection, particularly in the ways the drug are divided or prepared for injection.
Citations

1. AASLD-IDSA. Recommendations for testing, management, and treating hepatitis C. When and in whom to initiate HCV therapy. [AASLD-IDSA Hepatitis C Guidance] -

2. Center for Behavioral Health Statistics and Quality (CBHSQ), Substance Abuse and Mental Health Services Administration (SAMHSA), and U.S. Department of Health and Human Services (HHS). Results from the 2015 National Survey on Drug Use and Health:Detailed Tables [SAMHSA] -


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[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]


59. Purohit V, Rapaka R, Shurtleff D. Role of cannabinoids in the development of fatty liver
[PubMed Abstract] -

[PubMed Abstract] -

[PubMed Abstract] -

References

[PubMed Abstract] -

[PubMed Abstract] -

[PubMed Abstract] -

[PubMed Abstract] -

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[PubMed Abstract] -

[PubMed Abstract] -

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Figures

Figure 1 Adherence with HCV Therapy in C-EDGE CO-STAR Trial

In this trial, investigators evaluated HCV treatment with elbasvir-grazoprevir in 301 persons with a history of injection drug use who were receiving opioid agonist therapy (e.g. methadone, buprenorphine, or buprenorphine-naloxone maintenance) for at least 3 months prior to enrollment. This graph shows excellent rates of adherence.

This study enrolled 40 patients with hepatitis C (genotypes 1, 2, or 3) and injection drug use who received treatment with peginterferon (or interferon) plus ribavirin. Among individuals with drug abstinence for longer than 6 months prior to treatment, 50% achieved a sustained virologic response (SVR), compared with 63% for those with drug abstinence for 6 months or less (data not shown). Overall, the SVR rates with any drug use during hepatitis treatment (53%) did not appear different than with no drug use during treatment (57%), with the exception that SVR rates were very low with frequent drug use during treatment (22%).

**Figure 3 HCV Treatment Responses in 3 Treatment Eras in Patients with HIV Coinfection and Frequent Barriers to Care**

This graphic shows a retrospective comparison of SVR rates in three different HCV treatment eras in an urban HIV clinic where barriers to care, including drug and alcohol use were common.


<table>
<thead>
<tr>
<th>Treatment</th>
<th>SVR Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG + RBV</td>
<td>38.4</td>
</tr>
<tr>
<td>PEG + RBV + PI</td>
<td>48.0</td>
</tr>
<tr>
<td>INF-Free DAA</td>
<td>83.3</td>
</tr>
</tbody>
</table>

**Legend:**
- PEG = peginterferon
- RBV = Ribavirin
- PI = Protease Inhibitor
- INF = Interferon
- DAA = Direct-Acting Antiviral
Figure 4 (Image Series) - Elbasvir-Grazoprevir in Persons who Inject Drugs: C-EDGE CO-STAR (Image Series) - Figure 4 (Image Series) - Elbasvir-Grazoprevir in Persons who Inject Drugs: C-EDGE CO-STAR
Image 4A: SVR12 Results (Assumes Reinfections are Failures)


C-EDGE CO-STAR: SVR12 Results with Full Analysis Set

*Includes one subject with mixed infection (GT 1a and 1b) who achieved SRV12
Figure 4 (Image Series) - Elbasvir-Grazoprevir in Persons who Inject Drugs: C-EDGE CO-STAR
Image 4B: SVR12 Results (Assumes Reinfections are Responses)


C-EDGE CO-STAR: SVR12 Results with Modified Full Analysis Set^

<table>
<thead>
<tr>
<th>Patients with SVR12 (%)</th>
<th>All GT</th>
<th>GT1a*</th>
<th>GT1b</th>
<th>GT4</th>
<th>GT6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>189/198</td>
<td>147/153</td>
<td>28/29</td>
<td>11/11</td>
<td>3/5</td>
</tr>
</tbody>
</table>

^Excludes patients who discontinued trial for non-treatment related reasons
*Includes one subject with mixed infection (GT 1a and 1b) who achieved SRV12
Figure 4 (Image Series) - Elbasvir-Grazoprevir in Persons who Inject Drugs: C-EDGE CO-STAR
Image 4C: SVR12 by Subgroups


C-EDGE CO-STAR: SVR12 Results with Modified Full Analysis Set^*^

^*^Excludes patients who discontinued trial for non-treatment related reasons

![Graph showing SVR12 results by subgroups](image-url)
**Figure 5 Sustained Virologic Responses to Ledipasvir-Sofosbuvir in Persons Receiving Opioid Substitution Therapy: Phase 3 ION Trials**

Abbreviations: OST = opioid substitution therapy. This graph shows summary data from the phase 3 ION trials comparing SVR rates with ledipasvir-sofosbuvir for the small subset of persons enrolled in the trials who were receiving OST versus those not receiving OST.

Figure 6 Impact of Alcohol Consumption on HCV Treatment Response

In this study, investigators examined the impact of excessive alcohol consumption on hepatic fibrosis in patients with chronic hepatitis C infection. Excessive alcohol consumption was defined as more than 60 g/day for men and more than 40 g/day for women. Throughout all times during the study it was clear that patients with excessive alcohol ingestion had greater risk of developing cirrhosis.


*Excessive alcohol defined as > 40 g/day for women and > 60 g/day for men
Figure 7 Impact of Alcohol Consumption on HCV Treatment Response

Investigators enrolled 73 patients with chronic hepatitis C (genotypes 1-4) who had ongoing alcohol consumption (or abstinence for less than 6 months). All patients received peginterferon and ribavirin. Abstinence referred to patients off alcohol during the entire treatment period. Low risk consumption was defined as weekly consumption of no more than 21 standard drinks for men and 14 drinks for women, and no more than 4 by drinking occasion. Excessive consumption was defined as drinking more than the limits defined for low risk consumption on at least two occasions during the treatment period. Overall, 48% of the patients achieved an SVR. Patients with excessive alcohol use had lower SVR response rates than those who were abstinent or had low-risk ingestion.


Sustained Virologic Rates According to Alcohol Consumption During Therapy

<table>
<thead>
<tr>
<th>Alcohol Use During HCV Treatment</th>
<th>Patients with SVR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>43.0 (n = 73)</td>
</tr>
<tr>
<td>Abstinent</td>
<td>65.0 (n = 20)</td>
</tr>
<tr>
<td>Low Risk</td>
<td>52.2 (n = 23)</td>
</tr>
<tr>
<td>Excessive</td>
<td>33.3 (n = 24)</td>
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