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Title

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Authors

Benade, M
Rosen, S
Antoniak, S
et al.

RESEARCH

Impact of direct-acting antiviral treatment of hepatitis C on the quality of life of adults in Ukraine

M. Benade[1*], S. Rosen[1,2], S. Antoniak[3], C. Chasela[4,5], Y. Stopolianska[3], T. Barnard[6], M. M. Gandhi[7], I. Ivanchuk[8], V. Tretiakov[9], J. Dible[6], T. Minior[6], K. W. Chew[7], C. van der Horst[10^], Z. Tsenilova[11] and I. Sanne[2,4,12]

Abstract

Background: Direct-acting antivirals (DAAs) are highly effective in achieving sustained virologic response among those with chronic hepatitis C virus (HCV) infection. Quality of life (QOL) benefits for an HCV-infected population with high numbers of people who inject drugs and people living with HIV (PLHIV) in Eastern Europe have not been explored. We estimated such benefits for Ukraine.

Methods: Using data from a demonstration study of 12-week DAA conducted in Kyiv, we compared self-reported QOL as captured with the MOS-SF20 at study entry and 12 weeks after treatment completion (week 24). We calculated domain scores for health perception, physical, role and social functioning, mental health and pain to at entry and week 24, stratified by HIV status.

Results: Among the 857 patients included in the final analysis, health perception was the domain that showed the largest change, with an improvement of 85.7% between entry and week 24. The improvement was larger among those who were HIV negative (104.4%) than among those living with HIV (69.9%). Other domains that showed significant and meaningful improvements were physical functioning, which improved from 80.5 (95% CI 78.9–82.1) at study entry to 89.4 (88.1–90.7) at 24 weeks, role functioning (64.5 [62.3–66.8] to 86.5 [84.9–88.2]), social functioning (74.2 [72.1–76.2] to 84.8 [83.2–86.5]) and bodily pain (70.1 [68.2–72.0] to 89.8 [88.5–91.1]). Across all domains, QOL improvements among PLHIV were more modest than among HIV-negative participants.

Conclusion: QOL improved substantially across all domains between study entry and week 24. Changes over the study period were smaller among PLHIV.

Keywords: HCV, HIV, Treatment, PWID, Ukraine, Quality of Life

Background

Hepatitis C virus (HCV) infection remains a major public health concern globally, with 58 million people estimated to be living with chronic HCV infection and at high risk of developing liver cirrhosis, hepatocellular carcinoma,

liver failure, and death if left untreated [1–4]. DAA treatment, which cures HCV within 8–12 weeks, is now widely available in some countries [5]. Benefits in treating HCV are found in averted deaths, reduced morbidity, and improvement of reported QOL and economic productivity [6–9].

In Ukraine, it is estimated that 3.5% of the general population are living with HCV, of whom a large proportion are people who inject drugs (PWID) and many are co-infected with HIV [10]. Other high risk groups include

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^C. van der Horst—Deceased

*Correspondence: mbenade@bu.edu

[1] Boston University School of Public Health, Boston, MA, USA
Full list of author information is available at the end of the article

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sexual partners of those with HIV, sex workers, prisoners, military members, and populations in conflict zones [10]. Lack of adequate state funding, especially for diagnostics, presents a significant barrier to accessing treatment with DAA [11].

In 2018, a single-arm demonstration project was implemented to evaluate a scalable, integrated, low cost HIV and HCV testing and management intervention in Ukraine offering HCV treatment with sofosbuvir/ledipasvir for 12 weeks, with or without weight-based ribavirin (WBR) in Ukraine [12]. The study also collected data on participants' self-reported QOL at the start and end of the study period. The goal of our study is to report changes in QOL experienced between starting an effective 12-week HCV treatment regimen and 12 weeks after the end of that treatment.

Methods

Parent study
For the original demonstration study, patients were enrolled at two public clinics in Kyiv, Ukraine. Study sites, sample selection and data collection have been described previously [12]. Eligibility criteria included HCV viraemia, being treatment naïve and age ≥ 18 years, and no or compensated liver cirrhosis. Those eligible were offered HIV and HCV testing, 12-week treatment of HCV with DAAs supported by simplified HCV treatment monitoring, and initiation of HIV antiretroviral therapy (ART) for those with untreated HIV co-infection. The study's primary outcome was sustained virologic response (SVR) at 12 weeks after treatment completion (equivalent to 24 weeks after treatment initiation). Of the 868 participants enrolled, 860 completed the 24-week follow-up visit and were assessed for SVR. By intention-to-treat analysis, the overall treatment success rate was 95.7% (831/868) [12].

Quality of life data and analysis
Interviews were conducted at study entry and 24 weeks for QOL indicators, using an adapted version of the Medical Outcomes Study 20-Item Short Form Health survey (MOS SF-20) (Additional file 1) [13]. We compared QOL measures between baseline and endline for each question. We also aggregated responses according to MOS SF-20 categories of health perception, physical functioning, mental health, role functioning, social functioning, and bodily pain to assign a mean value for each category at baseline and endline, stratified by HIV status. Scores for each of the six subscales (physical, social and role functioning, pain, mental health, and health perception) were calculated as described by Stewart et al. [13]. In each domain, the lowest possible score was zero and the highest possible score was 100. We stratified the domain

scores by SVR and HIV status and performed t-tests to determine statistical significance in difference of means between baseline and endline, as well as by HIV status and major demographic characteristics (age, education, employment status, injection drug use status).

Results
Of the 868 patients who were included in the primary analysis, we assessed baseline data on all 868 and endline data on 857, with the discrepancy reflecting patients who did not complete the study or had substantial missing data on QOL variables. Detailed characteristics of enrolled participants, their clinical and laboratory outcomes, and the costs of the intervention to the provider are reported elsewhere [12] and summarized in Additional file 1: Table S1. The median (IQR) age of the population was 39 years (35–44) and 66% were male. Most participants identified as PWID (87%), of whom 95% self-reported being on medication-assisted therapy (MAT). Just over half the sample (482, 55%) were HIV positive; all were on ART at the time of study enrollment. The 11 patients who were excluded from the final analysis did not differ from those in the analysis in terms of employment status or education level; all those excluded identified as PWID; were younger than 45 years, did not have liver cirrhosis, and were more likely to be co-infected with HIV; and 90% were male (Additional file 1: Table S2).

Responses to all QOL questions at baseline and endline are reported in Additional file 1: Table S3. Below we highlight differences between the two periods in the six domains listed above.

Self-reported health
At study entry, 66% of participants reported their health as either "poor" or "fair". By study exit, 80% reported their health as "good", "very good" or "excellent." Consistent with this result, 73% of participants reported that their health was either "somewhat better" (43%) or "much better (30%) at 24 weeks than at study entry. The proportion of patients who agreed with the statement "my health is excellent" increased from 27% to 68% over the study period, while those agreeing with the statement "I have been feeling bad lately" decreased from 57% to 11%. The mean domain score for health perception increased from 33.7 (95% CI 32.4–35.1) at study entry to 62.3 (60.7–63.9) at 24 weeks (Fig. 1).

Physical activities, role, and social functioning
The proportions of participants who reported being limited in conducting a range of physical activities fell over the study period for all activities (Fig. 2). The largest difference was seen in vigorous activity, where the
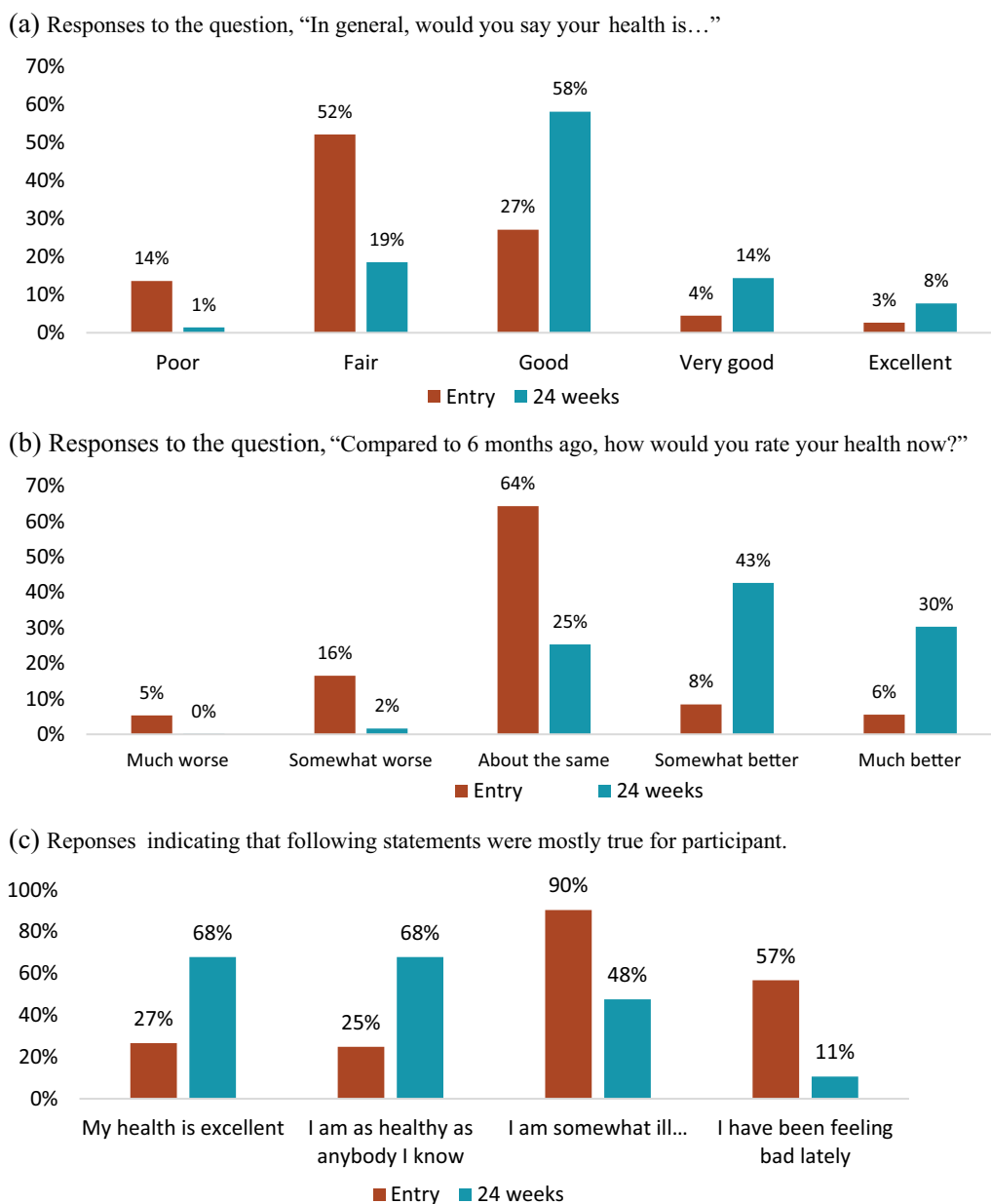
(a) Responses to the question, "In general, would you say your health is…"

(b) Responses to the question, "Compared to 6 months ago, how would you rate your health now?"

(c) Reponses indicating that following statements were mostly true for participant.

Fig. 1 Self-reported health at study entry (baseline) and 24 weeks

proportion who reported facing limitations declined from 54% to 32%. The mean domain score for physical functioning increased from 80.5 (95% CI 78.9–82.1) to 89.4 (88.1–90.7). Formal sector employment also rose over the study period, from 33% to 40% of the cohort. The proportion of participants who reported that their health affected "a lot" the quality at which they could perform their main activity decreased from 76% at study entry to 12% at 24 weeks. The mean number of days that participants were unable to perform their main activity due to

their health or seeking health care in the past 2 weeks decreased from 1.6 (95% CI 1.5–1.8) days to 0.8 (0.6–1.0) days over the study period. Finally, the mean social functioning score improved from 74.2 (95% CI 72.1–84.8) to 84.8 (83.2–86.5).

Mental health and symptoms
Questions related to anxiety and depression showed a substantial improvement in mental health over the study period (Fig. 2), with the mean score for the mental health
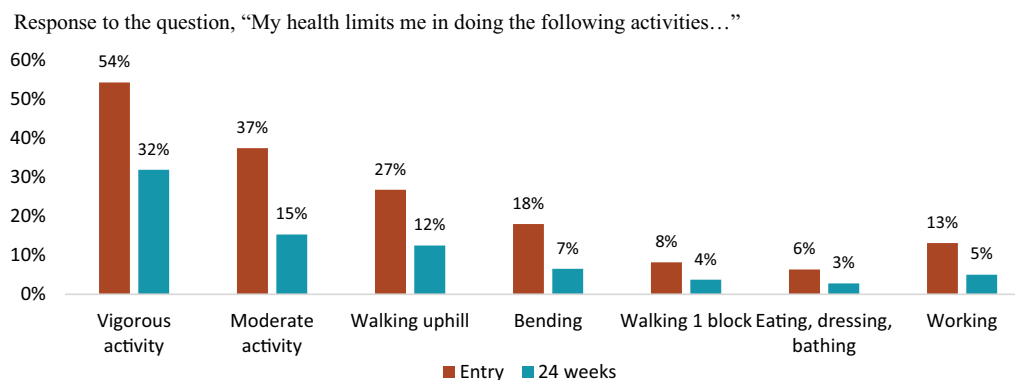
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Fig. 2 Functional impairment at study entry (baseline) and 24 weeks

domain increasing from 67.0 (95% CI 65.5–68.2) to 70.5 (69.1–66.9).

The proportion of patients who reported having no or very mild inability to focus increased from 54% at study entry to 77% at endline, while those who reported a moderate inability to focus decreased from 23% to 9%. An improvement in reported tiredness and fatigue was also observed, increasing from 21% who reported no or very mild fatigue at study entry to 62% at 24 weeks. Bodily pain improved from 50% reporting no or very mild body pain at initiation to 84% at study endline. The mean domain score for pain improved from 70.1 (95% CI 68.2–72.0) to 89.8 (88.5–91.1) over the study period.

Stratification by HIV status

Participants with HIV and those without did not differ at baseline for any of the domains (Additional file 1: Table S3). Domain scores reported at 24 weeks in the physical functioning domain were lower for PLHIV (87.4, 95% CI 85.5–89.4) than for those not living with HIV (91.9, 90.0–93.5). Improvements in the social domain were larger among those who were not living with HIV (87.7, 95% CI 85.5–89.9) than among those with HIV (82.5, 80.1–84.9). Similarly, health perception improved by a larger margin among those who were not living with HIV (67.9, 95% CI 64.5–70.3) than among those with HIV (57.7, 55.6–59.9). Role functioning was slightly higher among those not living with HIV (87.2 (95% CI 84.7–89.8) vs 85.8 (83.5–88.1)) and domain scores for pain and mental health were marginally higher among PLHIV, but these differences were not statistically significant.

Stratification by SVR

Participants who failed to achieve SVR at 24 weeks but did complete the 24 week-questionnaire (n = 18) data had higher baseline (study entry) domain scores across all domains except for the Mental Health domain

(Additional file 1: Table S3) than did those who achieved SVR. The patients who failed treatment, however, reported smaller changes in domain scores over the study period than did those with SVR. Among participants who failed to achieve SVR, health perception improved 65%, in comparison to 86% in the full cohort. Bodily pain improved by 15% among participants who failed to achieve SVR compared to 28% in the full study cohort. Other variables such as education, age, employment status and whether or not participant was considered PWID were also examined but there were no differences in these indicators between people with and without HIV.

Discussion

In this study of more than 850 HCV-infected adults in Ukraine, of whom most were PWID and over half had HIV, effective HCV treatment produced large gains in QOL across all measured domains. The greatest improvements between study enrollment (baseline) and 24 weeks (endline) were in health perception (+26.8), role functioning (+22.0), and pain (+19.7). Social functioning (+10.9) and physical functioning (+8.9) improved somewhat less but still showed significant improvement at endline compared to study entry.

The results we observed in this cohort in Ukraine were similar to or of greater magnitude than those reported from other settings [6, 14–16]. In a Japanese cohort, the only domain of the MOS SF-36 that was found to be significantly improved was general health perception, with an improvement of 3.81 that persisted at 3 years after treatment with DAA [6]. Younossi et al. found similarly that statistically significant, modest improvements in reported QOL were sustained as long as 2 years after SVR was achieved in U.S. patients [17]. The larger improvements we observed may reflect our relatively short follow up period (24 weeks after treatment initiation) and the fact that our study was conducted in a middle income

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country, rather than high income, and among many patients with co-morbidities; our participants had worse baseline domain scores and thus more room for HCV treatment to improve their QOL.

Our study had several limitations. Data were drawn from a single-arm implementation trial; we had no HCV-negative comparison population. Because the treatment success rate was so high, we also lack a large comparison group with those failing HCV treatment. It is possible that some of the improvements we observed would have come about anyway, without HCV treatment, though the relatively short interval between our baseline and endline interviews (24 weeks) makes major secular shifts unlikely and our limited data showed that participants who did not achieve SVR had smaller improvements in QOL over the study period and lower reported QOL at study end line. By definition, patients who were lost to follow up were missing endline data; if these patients were also sicker or more disabled by HCV than were those who did finish, our results would overestimate overall improvements. Comparison of the two groups at baseline, however, did not reveal any differences in their condition. Our choice of tool, the SF-20, is known to have floor effects for social functioning, bodily pain, and role functioning and ceiling effects across all domains reported. Finally, our endline measurement took place 12 weeks after treatment completion, and therefore findings are limited to short-term improvements in QOL only.

Despite these limitations, the large improvements we observed in QOL for this cohort of patients suggests that HCV treatment, as delivered in this intervention, has a major positive effect on the mental and physical well-being, self-perception, and productivity of those who complete treatment. While some of the impacts are slightly more modest for patients with HIV, general conclusions remain the same. These results add to the benefits of offering effective HCV treatment to all with active HCV infection.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-022-07615-9.

Additional file 1: Figure S1. Mental health at study entry (baseline) and 24 weeks. **Table S1.** Baseline characteristics of the cohort. **Table S2.** Baseline characteristics, final analytic sample, and participants excluded due to missing data. **Table S3.** Medical Outcomes Study 20-Item Short-Form Health Survey results per domain, entry (baseline) and 24 weeks, for full cohort and stratified by HIV status.

Declarations

Author details
[1]Boston University School of Public Health, Boston, MA, USA. [2]Health Economics and Epidemiology Research Office, Department of Internal Medicine, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa. [3]Right to Care, Kyiv, Ukraine. [4]Right to Care, Centurion, Pretoria, South Africa. [5]Department of Epidemiology and Biostatistics, School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa. [6]United States Agency for International Development, Washington, DC, USA. [7]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA. [8]Public Health Centre of Ministry of Healthcare of Ukraine, Kyiv, Ukraine. [9]100% Life, Kyiv, Ukraine. [10]University of North Carolina, Chapel Hill, USA. [11]Alliance for Public Health, Kyiv, Ukraine. [12]Department of Internal Medicine, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa.

References

1. World Health Organization (WHO). Progress Report on HIV, viral hepatitis and sexually transmitted infections 2019. accountability for the global health sector strategies, 2016–2021. Geneva: World Health Organization; 2019 (WHO/CDS/HIV/19.7). Licence: CC BY-NC-SA 3.0 IGO. https://apps.who.int/iris/handle/10665/324797. Accessed 16 Mar 2021.
2. Messina JP, Humphreys I, Flaxman A, et al. Global distribution and prevalence of hepatitis C virus genotypes. Hepatology. 2015;61(1):77–87. https://doi.org/10.1002/hep.27259.
3. Spearman CW, Dusheiko GM, Hellard M, Sonderup M. Hepatitis C. Lancet. 2019;394(10207):1451–66. https://doi.org/10.1016/S0140-6736(19)32320-7.
4. World Health Organization (WHO). Hepatitis C. https://www.who.int/news-room/fact-sheets/detail/hepatitis-c. Accessed 12 Jan 2022.

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5. Carrat F, Fontaine H, Dorival C, et al. Clinical outcomes in patients with chronic hepatitis C after direct-acting antiviral treatment: a prospective cohort study. Lancet. 2019;393(10179):1453–64. https://doi.org/10.1016/S0140-6736(18)32111-1.

6. Ichikawa T, Miyaaki H, Miuma S, et al. Direct-acting antivirals improved the quality of life, ameliorated disease-related symptoms, and augmented muscle volume three years later in patients with hepatitis C Virus. Intern Med. 2020;59(21):2653–60. https://doi.org/10.2169/internalmedicine.5102-20.

7. Nardelli S, Riggio O, Rosati D, Gioia S, Ridola L, Farcomeni A. Hepatitis C virus eradication with directly acting antivirals improves health-related quality of life and psychological symptoms. World J Gastroenterol. 2019;25(48):6928–38. https://doi.org/10.3748/wjg.v25.i48.6928.

8. Fagundes RN, de Castro Ferreira LEVV, de Lima Pace FH. Health-related quality of life and fatigue in patients with chronic hepatitis C with therapy with direct-acting antivirals agents interferon-free. PLoS ONE. 2020;15(8 August):e0237005. https://doi.org/10.1371/journal.pone.0237005.

9. Smith-Palmer J, Cerri K, Valentine W. Achieving sustained virologic response in hepatitis C: a systematic review of the clinical, economic and quality of life benefits. BMC Infect Dis. 2015;15(1):1–19. https://doi.org/10.1186/s12879-015-0748-8.

10. Devi S. Ukrainian health authorities adopt hepatitis C project. Lancet (Lond, Engl). 2020;396(10246):228. https://doi.org/10.1016/S0140-6736(20)31639-1.

11. Health TA for P. Over 5% of Ukrainians are infected with hepatitis C. Accessed March 16, 2021. https://aph.org.ua/en/news/over-5-of-ukrainians-are-infected-with-hepatitis-c/. **(Published 2016).**

12. Antoniak S, Charles Chasela C, Freiman MJ, et al. Treatment and cost-outcomes of a simplified antiretroviral treatment strategy for hepatitis C among HCV and HIV co-infected patients in Ukraine. medRxiv. 2021.03.19.21253780. https://doi.org/10.1101/2021.03.19.21253780. **(Published online January 1, 2021)**

13. Stewart AL, Hays RD, Ware JE Jr. The MOS short-form general health survey: reliability and validity in a patient population. Med Care. 1988;26(7):724–35. https://doi.org/10.1097/00005650-198807000-00007

14. Schulte B, Schmidt CS, Manthey J, et al. Clinical and patient-reported outcomes of direct-acting antivirals for the treatment of chronic hepatitis C among patients on opioid agonist treatment: a real-world prospective cohort study. Open Forum Infect Dis. 2020;7(8):ofaa317. https://doi.org/10.1093/ofid/ofaa317.

15. Thein H-H, Krahn M, Kaldor J. Estimation of Utilities for chronic Hepatitis C from SF-36 Scores Health Policy Gap analysis view project ethical aspects of infectious disease control view project. Artic Am J Gastroenterol. 2005. https://doi.org/10.1111/j.1572-0241.2005.40976.x (**Published online 2005**).

16. Serper M, Evon DM, Amador J, et al. Patient-reported outcomes 12 months after hepatitis C treatment with direct-acting antivirals: results from the PROP UP study. Liver Int. 2021. https://doi.org/10.1111/liv.14781 (**Published online January 2, 2021**).

17. Younossi ZM, Racila A, Muir A, et al. Long-term patient centered outcomes in cirrhotic patients with chronic hepatitis C after achieving sustained virologic response. Clin Gastroenterol Hepatol. 2021. https://doi.org/10.1016/j.cgh.2021.01.026.

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