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Cognitive Impairment and Cirrhosis in Older Patients: A Systematic Review

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Article

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Abstract

Prevalence of cirrhosis and hepatic encephalopathy (HE) in older patients receiving care in long-term care settings is unknown. This systematic review aimed to identify potential factors associated with HE and cognitive impairment in older patients with cirrhosis. A PubMed search of English-language articles published between January 1, 2000, and November 3, 2021, was conducted to identify studies in adults with cirrhosis relevant to cognitive impairment and/or HE (e.g., fall, frailty, and sarcopenia). Of 2,879 English-language publications, 24 were included. In patients with cirrhosis, falls were increased in the presence of HE and were associated with increased injury risk. Frailty was associated with HE development and cognitive impairment in patients with cirrhosis. Further, cognitive impairment and frailty were predictive of HE-related hospitalizations. Sarcopenia increased the risk of developing HE. Furthermore, specific medications increased the risk of developing HE. Risk reduction and management of patients with HE are critical to prevent negative outcomes.

Keywords

cognitive function, assisted living, long-term services and supports, hepatic encephalopathy

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Introduction

Cirrhosis is a chronic disease of the liver, characterized by pathophysiological changes related to increased hepatic resistance to portal blood flow, which occur due to both anatomical factors (e.g., angiogenesis and fibrogenesis) and functional abnormalities (e.g., endothelial dysfunction, decreased nitric oxide, and increased vasoconstrictor response; Tsochatzis et al., 2014). Overall US prevalence of cirrhosis is estimated at 0.24% to 0.27% (Scaglione et al., 2015, 2017). Given that cirrhosis is likely underdiagnosed and the increasing burden of nonalcoholic steatohepatitis-related cirrhosis and alcohol-associated liver disease, prevalence is likely to rise, particularly among an aging population with chronic liver disease (Estes et al., 2018; Mellinger et al., 2018); however, the prevalence of cirrhosis in older individuals is unknown. Progression from the asymptomatic, compensated phase of cirrhosis to the progressive, decompensated phase occurs with the onset of complications, such as ascites, variceal bleeding, and hepatic encephalopathy (HE) (D'Amico et al., 2006). Survival decreases with the transition from the compensated to the decompensated state (median survival, >12 years vs. 2 years, respectively; D'Amico et al., 2006). Patients with cirrhosis and their caregivers have reported care needs that include disease management (e.g., symptom monitoring, medication, and nutritional needs), psychosocial needs (e.g., depression and emotional distress), and financial issues related to reduced employment and increased medical costs (Ufere et al., 2020).

Cirrhosis has detrimental effects beyond the liver, including in the brain (Vilstrup et al., 2014). HE is a neurologic complication of cirrhosis characterized by manifestations ranging from subclinical (i.e., minimal HE [MHE], detected using psychometric testing) to motor (e.g., asterixis), behavioral (personality changes), and cognitive impairment (e.g., disorientation, lethargy, and confusion) and, in those most severely affected, coma (Vilstrup et al., 2014). Thus, a key component of the HE clinical spectrum is the associated cognitive

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impairment (i.e., cognitive impairment is a symptom or residual adverse outcome of HE). While the pathogenesis of HE is not entirely clear, HE occurs in patients with advanced liver disease and is believed to be caused by portosystemic shunting (Vilstrup et al., 2014). In 2018, 37.6% of patients developed HE <1 year after cirrhosis diagnosis (Potnis et al., 2021). Episodes of HE can be treated and resolve (Vilstrup et al., 2014), but patients with a history of HE have an increased risk of cognitive impairment (López-Franco et al., 2021). HE is a common cause of, and increases the risk of, hospital readmission in patients with cirrhosis (Shaheen et al., 2019; Tapper et al., 2016). However, HE-related readmissions are preventable (Volk et al., 2012).

Patients with cirrhosis transitioning to long-term care (LTC) facilities after hospitalization often have comorbidities (e.g., frailty and sarcopenia) and use multiple medications concomitantly, which potentially increase the risk of HE development and poor outcomes. At least 8.3 million individuals in the United States received care in an LTC setting in 2016 (Harris-Kojetin et al., 2019); however, prevalence of cirrhosis and HE in this setting is unclear. The introduction of an International Classification of Disease (ICD)-10 code specific for HE is anticipated in 2022 and may improve identification of patients with HE. This systematic review aimed to determine the association of factors likely to be of relevance in the LTC setting to the development of cognitive impairment and/or HE in older patients with cirrhosis.

Methods

A systematic review of PubMed of English-language articles published between January 1, 2000, and November 3, 2021, was conducted to identify factors associated with cognitive impairment and/or HE in patients with cirrhosis. Search terms included "hepatic encephalopathy," "cognitive dysfunction," "cognitive impairment," "cirrhosis," "liver disease," "falls," "frailty," "sarcopenia," "muscle wasting," "long term care facility," "nursing home," "skilled nursing facility," "elderly home," "residential care," "geriatric patients," "Medicare," "aged," and "elderly." Studies eligible for inclusion were those from North America and Europe that included patients aged ≥18 years with cirrhosis and reported outcomes related to falls, frailty, sarcopenia, and other factors identified in the literature search of relevance to cognitive impairment and/or HE. Studies were excluded if they did not report on patients with cirrhosis with HE and/or cognitive impairment, or report on the factors listed above. The title/abstract screening and subsequent full-text review of articles of interest were conducted by the authors.

Ratings of the quality of evidence for the studies presented were modified from the Oxford Centre for Evidence-Based Medicine (OCEBM Levels of Evidence Working Group) for ratings of individual studies, based on the following criteria (rating range, 1–5): 1 ("properly powered and conducted randomized clinical trial; systematic review with meta-analysis"); 2 ("well-designed controlled trial without randomization; prospective comparative cohort trial"); 3 ("case-control studies; retrospective cohort study"); 4 ("case series with or without intervention; cross-sectional study"); and 5 ("opinion of respected authorities; case reports").

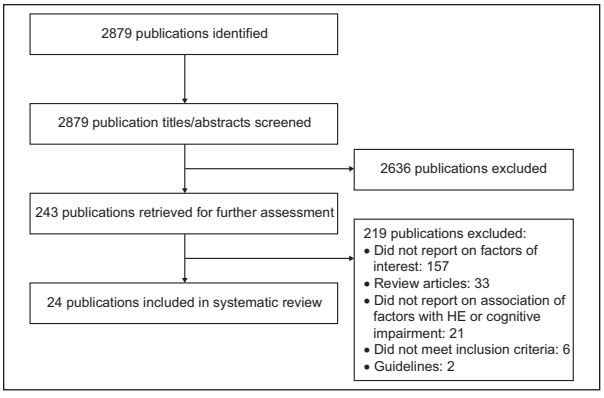

Figure 1. Selection of studies regarding factors associated with hepatic encephalopathy and cognitive impairment in cirrhosis.
Note. HE = hepatic encephalopathy.

Results

Of the 2,879 publications identified during initial literature review, 2,636 were excluded based on title and/or abstract review. Of the 243 publications retrieved for further review, 24 were identified for inclusion (Figure 1).

Falls

Six publications reporting on falls in patients with cirrhosis and HE-related outcomes were identified (Supplemental Table 1; Ezaz et al., 2018; Nardelli et al., 2021; Román et al., 2011; Soriano et al., 2012; Tapper et al., 2015, 2021). Of the three studies conducted in the United States, Tapper et al. (2021) reported that in outpatients with cirrhosis experiencing falls, the presence of HE increased the risk of mortality 4.2-fold. Ezaz et al. (2018) examined an emergency department (ED) database and reported that patients with cirrhosis and HE experienced severe fall-related injuries more often than patients with cirrhosis without HE; further, HE increased the risk of severe fall-related injury. Another study (Tapper et al., 2015) reported that 3.1% of hospital admissions (n = 1,749) in patients with cirrhosis were associated with a fall, and the incidence was found to be significantly higher in patients with HE compared with patients without HE (Tapper et al., 2015). Further, in this study, use of benzodiazepines and antipsychotics was associated with increased risk of falls and fall-related injuries (Tapper et al., 2015).

Of the three studies conducted in Europe (Supplemental Table 1), one that included mostly a population with

decompensated cirrhosis reported that cognitive dysfunction was observed in >40% of patients with a history of HE and falls, with ≥1 fall during the 1-year follow-up period (Soriano et al., 2012). Further, cognitive dysfunction was associated with greater fall frequency, and health care utilization for fall-related injuries was greater for patients with cognitive dysfunction than those without (Soriano et al., 2012). A second study, which examined the association of MHE with falls in patients with cirrhosis, reported that MHE, a history of HE, and antidepressant treatment increased fall risk (Román et al., 2011). Similarly, a third study reported that MHE and alterations in muscle quality and quantity increased the risk of falls in patients with cirrhosis (Nardelli et al., 2021). All studies related to falls received a rating of 2 ($n=3$ studies) or 3 ($n=3$ studies) for quality of evidence, given the prospective or retrospective design (Ezaz et al., 2018; Nardelli et al., 2021; Román et al., 2011; Soriano et al., 2012; Tapper et al., 2015, 2021). These study findings indicate that patients with cirrhosis with HE and/or cognitive impairment are at increased risk of falls and, potentially, fall-related injuries.

Frailty

Six publications associated with frailty in cirrhosis and HE were identified (Supplemental Table 2; Deng et al., 2021; Lai et al., 2019; Ney et al., 2018; Tapper, Derstine, et al., 2019; Tapper et al., 2018, 2020). Deng et al. (2021) reported that frailty was associated with moderate to severe clinical symptoms (e.g., fatigue, pain, and poor well-being) in patients with cirrhosis undergoing evaluation for liver transplantation and referral for palliative care; further, more patients who were frail had an increased prevalence of moderate to severe symptoms and reported a greater mean number of severe symptoms compared with robust patients and patients meeting criteria for prefrailty. However, presence of HE did not increase the odds of severe clinical symptoms (Deng et al., 2021). Indeed, in a subgroup analysis, a 0.5-unit increase (i.e., increasing frailty) in the Liver Frailty Index was significantly associated with severe symptoms in patients without HE ($n=190$; $p=.001$), but not in patients with HE ($n=43$; $p=.98$), suggesting that HE may drive symptoms reported by patients with cirrhosis, while frailty (in the absence of HE) may be an indicator of symptom burden (Deng et al., 2021).

The association between frailty (assessed by chair stands and grip strength) and the development of overt HE (OHE) in patients with cirrhosis was demonstrated by Tapper et al. (2020). A second study further supported the association between frailty (grip strength and chair stands) and cognitive function in patients with cirrhosis without current or history of HE (Tapper, Derstine, et al., 2019). Another study reported that frailty was associated with HE (i.e., walk speed and hand grip strength) in patients with cirrhosis undergoing evaluation for liver transplantation; further, walk speed was associated with mortality in patients with HE not receiving treatment for HE at the time of trial enrollment (Tapper et al., 2018). Lai et al. (2019) reported that patients with cirrhosis and HE on the liver transplantation wait list had increased odds of frailty compared with patients without HE; further, the 12-month wait list mortality rate was greater in patients with HE who were frail compared with patients with HE who were not frail. Finally, a composite assessment of cognitive impairment and frailty was predictive of HE-related hospitalizations within 6 months in patients with cirrhosis (Ney et al., 2018). All studies on frailty were prospective in nature, receiving a rating of 2 (Deng et al., 2021; Lai et al., 2019; Ney et al., 2018; Tapper, Derstine, et al., 2019; Tapper et al., 2018, 2020). Together, these findings indicate that frailty is associated with increased risk of OHE development in patients with cirrhosis, and frailty in the setting of cognitive impairment due to either HE or non–HE-related factors may have additive risk for cirrhosis-related hospitalizations and overall mortality.

Sarcopenia/Muscle Wasting

Seven publications examining HE-related outcomes and their association with sarcopenia and muscle wasting in patients with cirrhosis were identified (Supplemental Table 3; Al-Azzawi et al., 2020; Bhanji et al., 2018; Ebadi et al., 2020; Engelmann et al., 2018; Merli, Giusto, et al., 2013; Moctezuma-Velazquez et al., 2019; Nardelli, Lattanzi, et al., 2019). Ebadi et al. (2020) reported that severe sarcopenia occurred in a significantly greater percentage of patients with HE compared with nonsevere sarcopenia or no sarcopenia ($p=.001$). In a study of patients with alcoholic hepatitis, Al-Azzawi et al. (2020) reported that HE developed in a greater proportion of patients with sarcopenia compared with those without sarcopenia, and sarcopenia was associated with a 2.5-fold increased risk of developing HE ($p=.006$). Further, three independent trials reported that myosteatosis and/or sarcopenia were associated with development of HE (Bhanji et al., 2018; Moctezuma-Velazquez et al., 2019; Nardelli, Lattanzi, et al., 2019). Another trial showed that the paraspinal muscle index, but not the abdominal wall muscle index or skeletal muscle index, was predictive of development of HE in patients with cirrhosis wait-listed for liver transplantation (Engelmann et al., 2018). Finally, a trial that included hospitalized patients with cirrhosis demonstrated that muscle depletion (as shown by protein malnutrition) increased the risk for development of MHE and OHE (Merli, Giusto, et al., 2013). The quality of the evidence received a rating of 2 ($n=2$ studies) or 3 ($n=5$ studies; Al-Azzawi et al., 2020; Bhanji et al., 2018; Ebadi et al., 2020; Engelmann et al., 2018; Merli, Giusto, et al., 2013; Moctezuma-Velazquez et al., 2019; Nardelli, Lattanzi, et al., 2019). Overall, these data suggest that the risk of HE is increased in patients with cirrhosis with sarcopenia and/or myosteatosis.

Other Risk Factors of Potential Relevance in the Long-Term Care Setting

Five studies describing additional risk factors (e.g., comorbid conditions and medication use) were identified (Supplemental Table 4; Guevara et al., 2009; Labenz et al., 2020; Merli, Lucidi, et al., 2013; Nardelli, Gioia, et al., 2019; Tapper, Henderson, et al., 2019). Diabetes and hyponatremia were shown to increase the risk of OHE in patients with cirrhosis (Guevara et al., 2009; Labenz et al., 2020). In addition, bacterial infections increased the risk of subclinical and overt cognitive impairment in hospitalized patients with cirrhosis (Merli, Lucidi, et al., 2013). As well, certain medications associated with increased risk of developing HE in patients with cirrhosis were identified, including benzodiazepines, opiates, and proton pump inhibitors (Nardelli, Gioia, et al., 2019; Tapper, Henderson, et al., 2019). Benzodiazepines were also found to increase the risk of an HE-related hospitalization (Tapper, Henderson, et al., 2019). The studies were prospective ($n=4$) or retrospective ($n=1$) in nature, receiving a rating of 2 or 3, respectively, for quality of evidence (Guevara et al., 2009; Labenz et al., 2020; Merli, Lucidi, et al., 2013; Nardelli, Gioia, et al., 2019; Tapper, Henderson, et al., 2019).

Discussion

While the proportion of patients with cirrhosis who receive care in an LTC setting is currently unclear, given the aging population of patients with cirrhosis, many of whom have substantial medical comorbidities, it is important to better understand risk factors associated with worse outcomes in these older patients so that early and persistent interventions can be implemented to improve long-term outcomes. Existing data report on the overall burden of the aging US population with advanced medical illness, including dementia and impaired mobility, who will likely require some form of LTC services (Baughman & Hurdelbrink, 2018). Patients with cirrhosis are particularly vulnerable, especially those receiving care in LTC settings, given that their underlying liver disease and liver-related complications, such as HE, increase the risk of poor outcomes (e.g., falls and hospital readmissions). Thus, a better understanding of the potential risk factors associated with HE/cognitive impairment in patients with cirrhosis will help improve care of these patients in the LTC setting. In the United States (2018 data), unintentional falls occurred in 2.2 million individuals aged ≥65 years, with >650,000 falls resulting in hospitalization (Moreland & Lee, 2021). In an LTC setting (2015-2016 data), falls were reported in 21.5% and 16.1% of residents of care communities and nursing homes, respectively; a greater percentage of long-term nursing home residents experienced falls compared with short-term residents (19.1% vs. 13.5%; Harris-Kojetin et al., 2019). Further, a systematic review of community-dwelling older adults aged ≥65 years reported that falls ($n=10$ studies) and recurrent falls (i.e., ≥2 falls during a 0.5- to 1-year period; $n=12$ studies) were significantly associated with cognitive impairment (OR, 1.4 [95% CI, 1.1–1.6] and OR, 1.6 [95% CI, 1.3–1.9], respectively; Deandrea et al., 2010). The risk of fall-related injuries leading to readmission is high in patients aged ≥65 years, particularly in those with a history of falls and cognitive impairment (Hoffman et al., 2019). Findings of this systematic review suggest that interventions to prevent falls in patients with cognitive dysfunction or a history of HE and avoidance or limited use of some medications (e.g., benzodiazepines) may be warranted in an LTC setting (Román et al., 2011; Soriano et al., 2012; Tapper et al., 2015, 2021). Further, for patients with cirrhosis in LTC, thorough assessment and timely recognition of HE are important, given its association with cognitive impairment and risk of falls, and morbidity and mortality (Vilstrup et al., 2014).

In patients with cirrhosis, frailty was associated with HE and cognitive impairment (Deng et al., 2021; Lai et al., 2019; Ney et al., 2018; Tapper, Derstine, et al., 2019; Tapper et al., 2018, 2020). Indeed, a prospective study of adults aged ≥65 years reported overall cognitive function to be lower in those considered to be frail compared with those who were non-frail; further, cognitive function in the frail subgroup declined more than in the non-frail subgroup during a 5-year period (Chu et al., 2021). Frailty is prevalent in nursing home populations (63.6%), based on findings using a US database composed of Medicare/Medicaid-certified nursing home residents ($N=571{,}139$; Yuan et al., 2021). Further, cognitive impairment was associated with frailty, with individuals with moderate or severe impairment having a 35% (adjusted OR, 1.35; 95% CI, 1.33–1.37) and 74% (adjusted OR 1.74; 95% CI, 1.72–1.77), respectively, greater likelihood of being frail at time of nursing home admission compared with individuals who were not frail or had pre-frailty—these associations increased 3 and 6 months after nursing home admission (Yuan et al., 2021). Frailty, which is common in an LTC setting, is associated with HE and cognitive impairment in patients with cirrhosis; thus, these patients should be properly assessed and managed to minimize or prevent negative outcomes.

The important association between sarcopenia and the increased risk of HE in patients with cirrhosis, albeit across different study populations (e.g., geographic setting and patient setting), is highlighted in this current systematic review article (Al-Azzawi et al., 2020; Bhanji et al., 2018; Ebadi et al., 2020; Engelmann et al., 2018; Merli, Giusto, et al., 2013; Moctezuma-Velazquez et al., 2019; Nardelli, Lattanzi, et al., 2019). In patients with cirrhosis, development of alterations in both the quantity (i.e., sarcopenia) and quality (i.e., myosteatosis) of skeletal muscle has been associated with mortality (Hari, 2021; Montano-Loza et al., 2016). Indeed, a systematic review of six cohort and case-control trials

(up to 2018; $n = 1{,}795$ patients) reported that sarcopenia increased the odds of HE in patients with cirrhosis (OR, 2.7; 95% CI, 1.9–4.0; $p = .049$; Chang et al., 2019). As well, a second systematic review of three cohort, case-control, and cross-sectional trials of patients with cirrhosis (up to December 2018; $n = 1{,}547$ patients) determined that sarcopenia significantly increased the risk of developing HE in patients with cirrhosis (OR, 2.0; 95% CI, 1.3–3.3; Wijarnpreecha et al., 2020). The findings presented herein support that identification of patients with sarcopenia and/or introduction of interventions to improve the quality and quantity of skeletal muscle are warranted, given the increased risk of HE in patients with sarcopenia and/or myosteatosis (Al-Azzawi et al., 2020; Bhanji et al., 2018; Ebadi et al., 2020; Engelmann et al., 2018; Merli, Giusto, et al., 2013; Moctezuma-Velazquez et al., 2019; Nardelli, Lattanzi, et al., 2019).

Additional factors that increase the risk of HE development in patients with cirrhosis were also identified, including diabetes and hyponatremia, suggesting that a comprehensive approach to optimizing management of liver and non-liver comorbidities is an important strategy to help reduce the risk of OHE development (Guevara et al., 2009; Labenz et al., 2020). Bacterial infections increased the risk of subclinical and overt cognitive impairment in hospitalized patients with cirrhosis; thus, timely detection and treatment of infection in patients with cirrhosis to reduce the risk of secondary complications, such as HE, are paramount (Merli, Lucidi, et al., 2013). As well, certain medications were shown to increase the risk of developing HE in patients with cirrhosis (Nardelli, Gioia, et al., 2019; Tapper, Henderson, et al., 2019). Overall, while data are limited, it appears that optimizing management of comorbidities such as diabetes, recognizing and treating infections early and promptly, and minimizing or avoiding certain medications such as benzodiazepines are important for reducing the risk of HE or cognitive impairment in patients with cirrhosis.

A paucity of data specific to patients with cirrhosis in the LTC setting is a limitation of this systematic review. Further, studies available for inclusion differed in patient populations (e.g., inpatient, outpatient, and emergency department), study design (e.g., retrospective and prospective), and outcomes assessed (e.g., incidence and risk), limiting comparisons among studies (Al-Azzawi et al., 2020; Bhanji et al., 2018; Deng et al., 2021; Ebadi et al., 2020; Engelmann et al., 2018; Ezaz et al., 2018; Guevara et al., 2009; Labenz et al., 2020; Lai et al., 2019; Merli, Giusto, et al., 2013; Merli, Lucidi, et al., 2013; Moctezuma-Velazquez et al., 2019; Nardelli et al., 2021; Nardelli, Gioia, et al., 2019; Nardelli, Lattanzi, et al., 2019; Ney et al., 2018; Román et al., 2011; Soriano et al., 2012; Tapper, Derstine, et al., 2019; Tapper et al., 2015, 2018, 2020, 2021; Tapper, Henderson, et al., 2019). Definitions of sarcopenia were inconsistent among studies (Al-Azzawi et al., 2020; Bhanji et al., 2018; Ebadi et al., 2020; Engelmann et al., 2018; Merli, Giusto, et al., 2013; Moctezuma-Velazquez et al., 2019; Nardelli, Lattanzi, et al., 2019); indeed, in 2020, the Sarcopenia Definition and Outcomes Consortium published how best to define sarcopenia, which included muscle weakness (defined by low grip strength) and slowness (defined by gait speed; Bhasin et al., 2020). Management of falls and frailty in patients with cirrhosis is not necessarily different from management of these issues in the general LTC population. However, the early recognition of cognitive impairment, which can occur in the setting of cirrhosis masquerading as HE or may be further exacerbated by an acute episode of HE, is particularly important in patients with cirrhosis so that appropriate HE therapy can be provided if needed. The current systematic review highlights the potential importance of falls, frailty, and sarcopenia in patients with cirrhosis in the LTC setting and may be the impetus for future trials examining these factors and other outcomes in patients with cirrhosis and HE within this setting. However, given the large number of patients (including an unclear population of patients with cirrhosis) who receive care in an LTC setting, findings related to falls, frailty, sarcopenia, comorbid conditions, and medication use in older individuals with cirrhosis and cognitive impairment and/or HE are of clinical relevance and importance.

Reducing the risk for and recognition and timely and persistent management of HE in patients with cirrhosis is important for minimizing morbidity and mortality. Patients with cirrhosis are likely receiving care in the LTC setting, especially given the overall aging cirrhosis population with multiple concurrent comorbidities; thus, identification of potential factors associated with an increased risk of developing HE and cognitive impairment is paramount for implementing early interventions to improve outcomes in these patients. The findings of this systematic review reveal factors likely to be of relevance to older patients with cirrhosis in LTC facilities. As well, they emphasize the importance of timely and accurate assessment of cognitive impairment in patients with cirrhosis, careful assessment to elucidate whether underlying HE is masquerading as cognitive impairment, and effective linkage of identified patients with HE to appropriate treatment to improve patient outcomes.

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Author Contributions

Drs. Ohikere and Veracruz played a role in analysis and interpretation of the data, and preparation of the manuscript; Dr. Wong

played a role in study concept and design, acquisition of data, analysis and interpretation of data, and preparation of the manuscript; all authors approved the final draft for submission.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr. Ohikere reports having nothing to disclose. Dr. Veracruz reports having nothing to disclose. Dr. Wong reports receiving research grants (to his institution) and serving as a consultant and advisor to Gilead Sciences.

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Supplemental Material

Supplemental material for this article is available online.

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