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Topics in Antiviral Medicine™

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Invited Reviews CME

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Topics in Antiviral Medicine™

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On completion of this activity, which contains 3 articles, the learner will be better able to:

- Evaluate and safely manage chronic pain in older people with HIV
- Describe the interaction between HIV infection and age-related comorbidities, and conduct cognitive screening in older patients with HIV
- List patient experiences that have led to mistrust of vaccines and use humble inquiry to understand and discuss patients' concerns

Intended Audience

This enduring material is designed for physicians who are actively involved in the medical care of people with HIV and other viral infections.

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Invited Review

Chronic Pain and Opioid Use in Older People With HIV

Vasudev C. Mandyam, MD; R. Douglas Bruce, MD, MA, MS

Chronic pain is common among older people with HIV. Etiologies of chronic pain are multifactorial in this population. A careful and thorough initial assessment of pain is important. Associated conditions that can contribute to pain should be explored and managed as indicated. Special consideration is warranted for some of the unique aspects of pain in people with HIV. Chronic pain management is multimodal; a variety of pharmacologic and nonpharmacologic strategies are effective. Among medications, opioids can be used but carry a risk of significant harms. The use and monitoring of opioids is discussed here, and recommendations are made for the safe prescribing of opioids for chronic pain.

Keywords: HIV, chronic pain, opioids, older adults, aging

Introduction

Although chronic pain is prevalent among the general population, it is more common among people with HIV, especially among older people with HIV.[1-3]

Pain is a subjective experience. Although some organic processes generate pain, pain can be caused by a wide variety of pathologies and experiences, which complicates its evaluation and treatment. The underlying mechanisms of pain in people with HIV are multifactorial. Evaluating a person with HIV who has chronic pain requires a careful and thorough assessment. In this article, we have detailed approaches to treatment that begin with the assessment and evaluation of pain, management strategies in people with HIV, and the use and risks of opioids in this population.

Assessing and Evaluating Chronic Pain

People who present with a complaint of pain may often feel judged. Patients may fear that they will be seen as weak or unable to cope with the pain. They may also fear that the health care practitioner will assume that they are faking pain in search of medications. As a result, it is important to begin by validating the patient's complaint of pain: "I am so sorry to hear that you are experiencing this pain." Although acute pain may present, for example, with a swollen, erythematous joint, chronic pain does not necessarily present with objective evidence of pain. Patients with "silent" chronic pain can feel dismissed by others; providing validation can lead to improvement in attitudes and approaches to their symptoms.[4]

Pain influences and is influenced by a variety of individual factors. These can include depression, post-traumatic stress, substance use disorders, sleep disturbance, reduced antiretroviral adherence, missed HIV clinic visits, and unemployment.[5]

Taking a detailed history and conducting a proper physical examination are crucial to the accurate assessment of pain.[6] Medical and psychiatric evaluation can provide evidence of comorbidities, which can contribute to the perception and severity of pain, as described previously. Quality of life assessment is important, as is screening for substance use disorders.

Formulating a diagnosis is an important next step. This can be difficult in the setting of the multifactorial nature of pain. Pain sources include neuropathic, musculoskeletal, inflammatory, and visceral processes. The use of opioids for pain management can itself lead to pain, caused in part by the adaptation of opioid receptors over time. These and other factors should be considered when formulating a diagnosis.

Frequent reevaluation over time provides information about the progression of pain, response to treatment, and clues for alternate or new interim diagnoses. The Pain, Enjoyment, General Activity (PEG) scale is an easy-to-use 3-item scale that monitors pain severity and impact longitudinally. It is brief enough for practical use in clinical settings. By tracking the patient's PEG score, the practitioner can monitor and assess the response to treatments over time (Figure).[7] Furthermore, re-evaluations are too often simply an endorsement of the current treatment plan, and this approach can miss opportunities to confirm or modify a diagnosis as new data are available. Repeating examinations can bring to light changes that warrant further investigation. For example, a patient may have worsening lower back pain that is being treated as a flare of a musculoskeletal problem, but reexamination may reveal it is actually rheumatologic in nature.

HIV has unique pathophysiologic mechanisms that cause chronic pain; therefore, the evaluation of pain in people with HIV warrants added considerations.[8] The HIV-1 virus itself has neurotoxic effects, Proteins expressed by the person with HIV can lead to an increase in inflammatory cytokines; activation of the immune system stimulates nociceptors. Medications that treat HIV also can have neuropathic

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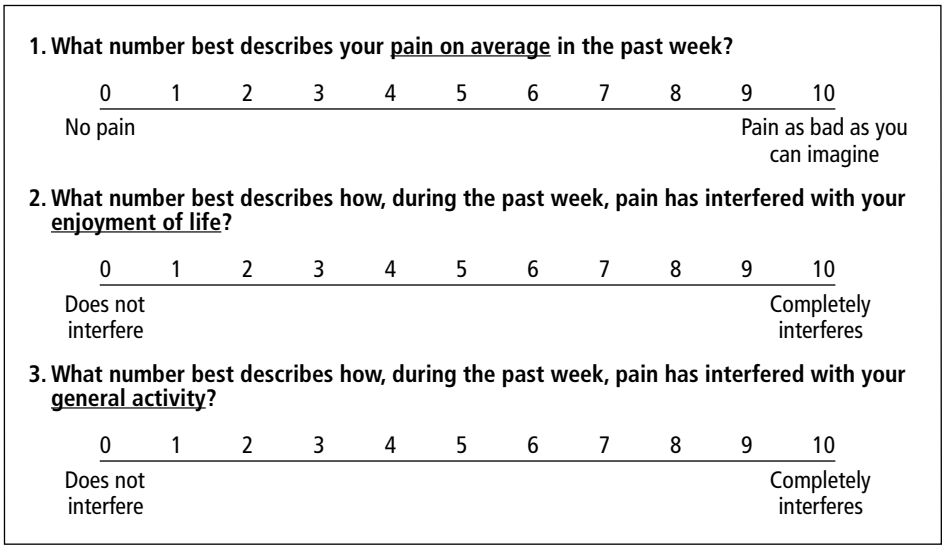

Figure. Pain, Enjoyment, General Activity (PEG) scale. Medical practitioners can use this scale to evaluate the severity of a patient's pain over time and adjust treatment accordingly. Adapted from Krebs et al.[7]

adverse effects. As a result, chronic pain remains a significant problem in people with HIV and is associated with functional impairments and reduced quality of life.

Management of Chronic Pain in Older People With HIV

Treatment for pain is multidisciplinary and multimodal. The Infectious Diseases Society of America (IDSA) has published clinical practice guidelines on the management of chronic pain in people with HIV, including older people.[9] This and other guidelines emphasize a multidisciplinary approach. In addition to the patient's primary prescriber, the treatment team can include a mental health clinician, case manager, pain specialist, physical therapist, acupuncturist, peer support, and others.

A variety of nonpharmacologic treatments have also been studied and are recommended. Cognitive behavioral therapy is one treatment modality that has been shown to improve adaptive behaviors to pain and subsequent outcomes. Interventions such as yoga, physical therapy, and acupuncture may also provide benefit.

Because HIV itself can injure nerves and create pain, the use of antiretroviral therapy may treat and prevent HIV-associated neuropathy. Gabapentin is an anticonvulsant medication used in a variety of applications, including a wide range of chronic pain conditions. Efficacy is questionable for many of the conditions in which gabapentin has been commonly used, but it is recommended for treatment of HIV-associated neuropathic pain. Gabapentin can cause sedation, which can be beneficial for people with insomnia, but it can also increase the risk of adverse events. Neuropathic medications such as tricyclic antide pressants, serotonin norepinephrine reuptake inhibitors, and pregabalin may also be used. Other beneficial agents include topical capsaicin, alpha-lipoic acid, and medical cannabis. Non-neuropathic pain can be managed with acetaminophen and nonsteroidal anti-inflammatory drugs.

Opioids in Chronic Pain Management

Though they carry serious risks, opioids do play a role in the management of chronic pain in people with HIV. Opioids require close monitoring given the risk of developing opioid use disorder, and this monitoring is an important part of ongoing chronic pain management.

Given the risk of addiction, an opioid agonist should not typically be used as a first-line agent. The multimodal approach described in the prior sections is important for initial management and, if opioids are added, as an ongoing foundation in conjunction with the opioid therapy. Before the patient starts opioids, it is valuable to estimate the patient's baseline risk of developing harms or opioid use disorder. A variety of tools and calculators have been created to assist with this, including the Screener and Opioid Assessment for Patients with Pain (SOAPP), the revised SOAPP (SOAPP-R),[10] and the Opioid Risk Tool (ORT) (Table).[11]

The Centers for Disease Control and Prevention (CDC) has published a guideline for prescribing opioids for chronic pain.[12] This guideline provides several helpful strategies on how to safely select a patient who may benefit from opioids, start that patient on opioids, and monitor the patient for

Table. Opioid Risk Tool (ORT). A person's total score on an ORT assessment helps calculate their baseline risk of developing harms or an opioid use disorder (≤3 = low risk; 4-7 = moderate risk; ≥8 = high risk). Adapted from Webster et al.[11]

Mark each box that applies	Female	Male
Family history of substance abuse		
Alcohol	1	3
Illegal drugs	2	3
Prescription drugs	4	4
Personal history of substance abuse		
Alcohol	3	3
Illegal drugs	4	4
Prescription drugs	5	5
Age between 16-45 years	1	1
History of preadolescent sexual abuse	3	0
Psychologic disease		
Attention deficit disorder, obsessive-compulsive disorder, bipolar disorder, schizophrenia	2	2
Depression	1	1
Scoring totals		

harms. When patients have moderate-to-severe pain that has not responded to first-line and second-line therapies, opioids can be started as a time-limited trial. Practitioners should start with the lowest effective dose and exercise caution when increasing the dose. The use of morphine milligram equivalents (MME) is a common measure of the overall daily strength of a patient's opioid regimen. The measure is calculated by summing up the total dose of all opioids prescribed in a 24-hour period and converting this total to the equivalent amount of oral morphine. The CDC has resources to help with this calculation.[13] A dose higher than 50 MME/day can increase the risk of overdose and warrants close attention. Immediate-release, rather than extended-release, preparations may provide faster relief and can be titrated with a lower risk of overdose than longer acting medications. An important caution is that fast-acting opioids with short half-lives may carry an increased risk of abuse. Extended-release opioids should only be considered for patients who have severe continuous pain and who have been stabilized on an immediate-release medication first. Close interval follow-up should be arranged to evaluate the response to therapy and any adverse effects.

The pharmacodynamic effects of some medications change as people age. Many of the psychotropic effects are augmented in older adults. Older patients are also at increased risk of medication-induced confusion and delirium. In particular, opioids may carry an increased risk of medication-related adverse effects in older people. As an example, tramadol, a weak opioid with inhibitory activity on serotonin and norepinephrine reuptake, has been reported to cause severe hyponatremia, mostly in women above the age of 65 years in the initial week of therapy.[14] In addition to the pharmacodynamic effects, older adults with HIV are often on multiple medications. This polypharmacy, plus age-related changes in metabolism,[15] can result in unpredictable pharmacokinetic interactions, which may increase the risk of respiratory depression or other adverse events (eg, QT corrected for heart rate prolongation). Therefore, it is prudent when starting an older patient on an opioid to begin at the lowest dose and the longest intervals for dosing. Titration of the medication should account for the medication's half-life and the time to reach steady state, with repeated monitoring of the patient to avoid an adverse outcome. If practitioners are unclear on the timing of dosing or the rate of titration, they should consider speaking with pharmacy staff or reaching out to pain management specialists.

The use of patient–practitioner agreements, also known as controlled substance agreements or "pain contracts," is common for people on long-term opioid therapy. These are used for shared decision making and informed consent. Patients should be explicitly counseled on the risks and harms of opioids, including overdose and addiction. Assigning responsibility to the patient to self-monitor for the development of harms can be empowering to the patient, and it can help to focus on patient safety and risk–benefit analysis rather than on assigning blame. The practitioner, however, should keep in mind that HIV can be a proxy for risk-taking behavior. A person started on opioids should always be monitored for safety, and someone with a history of risk-taking behavior may be particularly vulnerable to taking risks with opioids as well.

Consideration should be given to prescribing intranasal naloxone as a rescue medication in case of overdose. Risk factors for overdose include a higher total opioid dose, concurrent use of other sedating medications such as benzodiazepines, history of substance use disorder, and comorbid medical conditions that can decrease clearance of medications (eg, liver and kidney disease) or increase risk of respiratory depression (eg, obstructive lung disease).

Urine toxicology is a widely used tool in monitoring for harms from opioids. The goal of urine drug testing (UDT) is to detect the presence of prescribed substances and to screen for the presence of nonprescribed substances. UDT should be performed with open communication about the intent, namely as a monitoring tool for a potentially harmful treatment, rather than as an attempt to catch bad behaviors. There are limited data regarding the efficacy and optimal frequency of UDT in detecting concerns for the patient's treatment. Interpretation of UDT can be complicated and requires knowledge of drug metabolites, assay interference, and false positives and negatives. For example, the ingestion of poppy seeds has the potential to cause low levels of morphine in the urine, which prompted most immunoassays to move from 100 ng/mL to 300 ng/mL for thresholds for a positive opiate urine test. Another example in some laboratories is the use of trazodone, which can cause a false positive amphetamine assay. When a false positive result is suspected, immunoassay tests can be sent for confirmation testing with gas chromatography and mass spectroscopy. Major management changes should not be made based solely on initial UDT results without further investigation.

There are other tools used for monitoring the safety of opioids. Prescription drug monitoring program (PDMP) data at the state level help look for inconsistencies in prescription-filling patterns. Pill counts can detect an escalation in a patient's dosage beyond prescribed limits, or they can detect a diversion of their medication.

Aberrant behaviors can be challenging to address. They may arise from an unrecognized substance use disorder, but they may also be due to inadequately managed pain and poor coping skills. The response to aberrant behaviors should be individualized and should take into account patient-specific factors and the overall safety profile of opioid treatment. It is very important that hospital and clinic staff feel safe and protected; in rare cases, a patient may be discharged from a clinic due to their behavior, but all efforts should be taken to address the situation first.

If routine close monitoring reveals concerns for an opioid use disorder, a thoughtful, patient-centered approach

is recommended. This includes consultation with practitioners who have expertise in the management of substance use disorder. Practitioners should continue to treat chronic pain and support the patient, even when discontinuing the opioid is the safest choice. In most cases, an opioid taper should not be initiated abruptly or unilaterally by the prescriber; a taper plan should instead be formulated with the patient's input and, depending on the situation, may require a slow, prolonged taper. There are exceptions where a rapid taper may be appropriate, such as the safety of a patient at acute risk of overdose. If the taper plan is not successful, consultation with or referral to a pain or addiction specialist is appropriate.

Conclusion

Older people with HIV have a high burden of chronic pain due to a variety of factors. It is important to inquire about chronic pain as it can impact health outcomes. Management of chronic pain requires a multimodal approach including both pharmacologic and nonpharmacologic interventions. Opioids can play a role among medications that manage chronic pain, and given their potential for significant harms, practitioners should be familiar with their use and understand how to monitor them.

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Invited Review

Neurocognition and the Aging Brain in People With HIV: Implications for Screening

Phillip Chan, MBChB, PhD; Victor Valcour, MD, PhD

The introduction of effective antiretroviral therapy (ART) has converted HIV infection from a lethal disease to a manageable chronic condition for most people. The drastic improvement in life expectancy of people with HIV has led to an expansion of the aging population of people with HIV globally. Recent research indicates that people with HIV on suppressive ART still sustain persistent, albeit alleviated, systemic and cerebral immune activation that can facilitate age-related causes of cognitive impairment (CI), including neurodegenerative and cerebrovascular diseases. Although HIV-associated neurocognitive disorder remains prevalent in older people with HIV on suppressive ART, the co-occurrence of other age-related causes of CI makes the investigation and management of CI more challenging. More importantly, it remains unknown if the neuropsychiatric manifestations of HIV-associated neurocognitive disorder are modified by the presence of age-related causes of CI, such as Alzheimer disease, and vice versa. This article will review findings regarding the interaction between HIV-1 infection and age-related comorbidities, namely atherosclerosis and neurodegenerative diseases, followed by cognitive outcomes of people with HIV in longitudinal studies. Cognitive symptoms of people with HIV on stable ART will be discussed. The review will go through the latest recommendations for cognitive screening in different HIV management guidelines, as well as the usefulness of various screening tools in the setting of stable viral suppression.

Keywords: neurocognition, HIV, screening, HAND, cognitive impairment, aging

Introduction

The availability of effective antiretroviral therapy (ART) has converted HIV infection from a lethal disease to a manageable chronic condition. People with HIV on stable and suppressive ART now enjoy a life expectancy comparable to HIV-uninfected populations. This drastic change in longevity has given rise to an upsurge of populations of aging people with HIV. Globally, around one-fifth of people with HIV are age 50 years or older, and the frequency of people with HIV age 50 years or older in the United States has been greater than 50% for many years. This demographic change has led to a shift in the focus of medical care and research from the management of immunodeficiency and opportunistic infection to that of noncommunicable diseases, particularly age-related comorbidities.

Cognitive impairment (CI) has been one of the more common complications among people with HIV since the pre-ART era. Before the availability of ART, AIDS dementia complex (ADC) was commonly seen in people with HIV of advanced immunodeficiency. In the current era, the frequency of HIV-associated dementia (HAD), an equivalent diagnosis to ADC, but employing the contemporary "Frascati" research criteria for HIV-associated neurocognitive disorder (HAND),[1] has dropped from about 15% to less than 5%, particularly among those on suppressive ART. Despite this, milder forms of HAND, namely asymptomatic neurocognitive impairment (ANI) and mild neurocognitive disorder (MND), remain common and range from 30% to 60% in studies with people with HIV on ART. However, these figures were largely based on samples of younger individuals. The prevalence and incidence of CI are likely to rise with aging, when other age-related causes of CI, namely neurodegenerative diseases and cerebrovascular diseases, unfold.

In younger people with HIV, the diagnosis of HAND is largely based on the exclusion of other etiologies. In older people with HIV, the co-occurrence of other age-related causes of CI could make the investigation and management of CI more challenging. In particular, existing studies support a view that HIV infection could lead to premature and accelerated cognitive aging among those who are older now and who have had an extensive duration with HIV, sometimes without suppression of HIV RNA.[2] Moreover, it remains unknown if the neuropsychiatric manifestations of HAND are modified by age-related causes of CI, and vice versa. Cognitive screening tools that work well for common neurodegenerative diseases may not have the same performance characteristics among people with HIV given the frequent cognitive inefficiency related to HIV, which can lead to abnormalities in testing performance across multiple domains. Furthermore, there is growing concern that incomplete immune recovery and persistent inflammation in people with HIV on suppressive ART could potentially fuel age-related

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processes, including atherosclerosis and neurodegenerative diseases.

Vascular Diseases in People With HIV in the ART Era

In the past, vascular dementia was narrowly defined as the cognitive decline seen after a documented stroke. More recent research highlights the important relationship between vascular pathology and cognitive decline.[3] Indeed, over 75% of aging brains show evidence of vascular pathology at autopsy, and both Alzheimer disease (AD) and vascular pathologies are key predictors of CI in the elderly. Cerebral small vessel disease has been associated with HAND in people with HIV. Compared with individuals without HIV, people with HIV have about 2-fold increased relative risk (RR) of coronary artery disease and 3-fold increased RR of stroke. In a systematic review of 80 longitudinal cardiovascular disease (CVD) studies, the global burden of HIV-associated CVD has tripled over the past 2 decades,[4] highlighting the persistent threat of CVD in people with HIV in the ART era. Data from Denmark and the United States suggest that people with HIV have a 1.6-fold to 2-fold increased risk of stroke compared with individuals without HIV, after adjustment of confounding factors.

HIV infection likely modifies atherosclerosis, one of the most important contributors of cerebrovascular diseases. Structurally, noncalcified coronary plaques are more prevalent in people with HIV than in individuals without HIV. Recent research highlights the association between atherosclerosis, persistent systemic immune dysregulation, and HIV reservoir. Monocyte/macrophage activation, denoted by elevated levels of plasma sCD14 and sCD163, and reversed CD4/CD8 ratio, a marker of T-cell dysregulation, is associated with atherosclerosis in people with HIV. Both conditions persist despite viral suppression.

HIV-encoded proteins, including transactivator of transcription (Tat), negative factor (Nef), and envelope protein gp120, are linked to inflammation, endothelial dysfunction, and endothelin-1 production.[5] Notably, the HIV reservoir is still able to produce HIV-encoded proteins through low-level transcription during plasma viral suppression. Increased microbial translocation in the gut, which persists during HIV suppression, serves as an important potential contributor to atherosclerosis, even among HIV-uninfected populations.[6] Apart from abnormal vascular wall inflammation detected by vascular positron emission tomography (PET) imaging, preclinical atherosclerotic changes of small-to-medium–sized intracranial arteries were readily detected in people with HIV within the first 6 years of HIV infection in autopsy,[7] suggesting that ART reduces inflammation but does not resolve arterial remodeling.

The elevated risk of atherosclerosis in treated people with HIV thus leads to the hypothesis that HAND persistence in the ART era might originate from vascular diseases.[8] In studies to date, HIV serostatus inconsistently serves as an independent risk factor linking atherosclerosis and CI. Nonetheless, HIV serostatus is strongly associated with metabolic risk factors of atherosclerosis, namely diabetes and hyperlipidemia. Future studies could clarify whether HIV infection is an independent risk factor of atherosclerosis and examine the longitudinal impact of atherosclerosis on the burden of vascular pathology and cognitive function in people with HIV.

HIV Infection and Neurodegenerative Diseases

In HIV-uninfected populations, systemic inflammation is a predictor of age-related cognitive decline. Systemic inflammatory scores built from levels of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), albumin, and iron predicted longitudinal cognitive outcomes in older adults. In another study, a combination of blood fibrinogen, white blood cell count, von Willebrand factor, and factor VIII, and CRP at midlife was predictive to cognitive change over 20 years. In people with HIV, recent research has indicated the persistence of cerebral inflammation despite suppressive ART, evidenced by elevated inflammatory and neuronal injury markers in the cerebrospinal fluid (CSF), abnormal central nervous system (CNS) metabolites in magnetic resonance spectroscopy, and abnormal activation signal in brain PET scans us ing macrophage/microglia-specific ligands. Moreover, elevated immune activation markers were associated with impaired cerebral white matter (WM) integrity, represented by lower fractional anisotropy and higher mean diffusivity in diffusion tensor imaging, in people with HIV. The latter was linked to worse cognitive speed and executive functions, and worse global cognitive performance.[9]

Whether persistent cerebral inflammation might accelerate or augment the cognitive symptoms among those with underlying neurodegenerative disease, such as AD and Parkinson disease (PD), remains inconclusive. Although there are reports that some people with HIV and CI have alterations of CSF biomarkers of AD including beta-amyloid and tau levels, recent PET studies do not show major differences in amyloid deposition stratified by HIV serostatus or HAND severity. However, no study to date compares the progression of cognitive decline or the change in AD-related biomarkers in AD-positive individuals with and without concomitant HIV infection. To date, only a handful of case reports have described diverse neuropsychiatric manifestations of individuals with HIV who presented with AD; some of them were pathologically confirmed.

Neurocognitive Outcomes in People With HIV on Suppressive ART

HIV enters the CNS within days after transmission. Impaired cognitive performance and depression symptoms are frequent among individuals who were recently infected during acute HIV. Without ART, cognitive deficits often develop and progress in a pattern that some have described as "subcortical," affecting psychomotor speed, information processing, executive function, and working memory, in addition to the

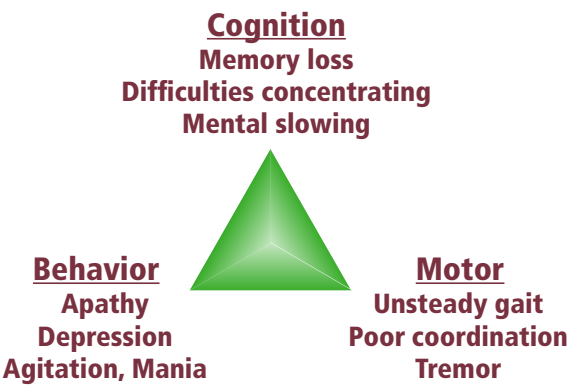

Figure. Clinical symptoms seen in the setting of HIV. Although individuals with HIV often present with memory complaints, careful questioning often identifies challenges with attention and concentration, as well as symptoms in the motor and behavioral domains.

psychiatric symptoms (Figure). In the pre-ART era, CI in people with HIV predominantly affected motor skills, cognitive speed, and verbal fluency, whereas those with HAND in the ART era demonstrate an increased association with memory (learning) and executive function deficits.[10] Women with HIV on suppressive ART share a similar profile of cognitive deficits. In a study with 239 middle-aged, virally suppressed women, participants with HIV scored lower in tasks involving learning, memory, attention, working memory, and fluency than HIV-uninfected controls. Two European cohort studies (COBRA [Comorbidity in Relation to AIDS] and POPPY [Pharmacokinetic and Clinical Observations in People Over Fifty]) targeting middle-aged people with HIV on suppressive ART showed worse performance in attention, executive function, psychomotor speed, and verbal learning than matched HIV-uninfected controls. Taken together, these studies revealed a mixed pattern of subcortical and cortical cognitive findings among aging people with HIV in the ART era. Clinically, poor memory may be the most common complaint of people with HIV with CI, despite testing that reveals learning inefficiency, attentional deficits, and executive challenges rather than deficits in encoding new memories. Closer inspection of the actual symptoms may reveal a mix of symptoms, including attentional deficits such as rereading of information to understand it and better recall with cues, as well as working memory and executive function challenges revealed through symptoms of difficulty in holding memory during multitasking.

The stability of cognitive function post-ART is another focus of HAND research. In an initial report from the CHARTER (CNS HIV Antiretroviral Therapy Effects Research) cohort that included 226 cognitively normal and 121 participants with ANI, those with ANI demonstrated a 2-fold to 6-fold increased risk of becoming symptomatic compared with cognitively normal participants at follow-up. In the MACS (Multicenter AIDS Cohort Study) investigation, the frequency of HAND increased from 25% to 31% among 197 individuals with HIV after 5 years of follow-up between 2007 and 2012. During the study period, 77% of the participants remained at the same stage, 13% deteriorated, and 10% improved. However, the 2 studies were limited by participants' inconsistent treatment and virus suppression status.

A follow-up cognitive trajectory analysis from the CHARTER cohort revealed that participants with declining cognitive trajectory were older, had worse baseline cognitive performance, and had a longer duration of HIV infection. In an Australia-based longitudinal study with 96 people with HIV on suppressive ART, only 16% showed cognitive decline over the study period of 18 months: 13% had either a history of HAND or baseline CI, compared with 3% who had neither condition. The rate of cognitive decline is similarly low in cohort studies of middle-aged people with HIV. A recent report from the HAILO (Long-term Follow-up of Older HIV-Infected Adults in the ACTG: Addressing Issues of Aging, HIV Infection, and Inflammation) study, which included 929 people with HIV at a median age of 51 years, identified CI in 16% of the participants at study baseline, whereas the development of CI over 3 years was 6%. A longitudinal report from the COBRA study revealed generally stable cognitive performance in virally suppressed people with HIV in comparison with the HIV-uninfected control over 2 years.

Longitudinal studies also shed light on the stability of different cognitive domains in people with HIV on suppressive ART. In the trajectory study of CHARTER, executive and motor functions, examined by the Trail Making Test B and the dominant hand grooved pegboard test, were the most common domains with decline over time. In contrast, no participant showed a decline in performing tasks related to verbal fluency (letter and category) and memory recall (verbal and nonverbal). Among virally suppressed people with HIV, subclinical decline in psychomotor speed and executive functioning were reported in the Australian cohort study, whereas a greater decline in motor skills was reported in the WIHS (Women's Interagency HIV Study) investigation that compared women who are virally suppressed and women without HIV. In short, longitudinal studies confirm the higher risk of cognitive decline in those with pre-existing CI or history of HAND; however, the rate of advanced impairment seen in dementia remains very small. In contrast, people with HIV without pre-existing CI or history of HAND demonstrated stable cognitive performance after suppressive ART. Among cognitive domains, declines in executive, motor, and psychomotor functions are the most common. In the authors' experiences, cognitive statuses of people with HIV suffering from concomitant HAND and AD usually deteriorate over 2 to 3 years, whereas cognitive statuses of those with HAND alone fluctuate without persistent decline.

Intraindividual Variability as a Marker of Cognitive Deficit in People With HIV

Apart from persistent, sometimes progressive CI that manifests as persistent cognitive deficits, older people with HIV

who have HAND often report fluctuation in cognitive symptoms, a finding that would not be surprising given the links between inflammation and cognitive performance. Indeed, some studies document fluctuating cognitive performance in people with HIV, as noted in the 2007 Frascati criteria.[1] Such fluctuations may present as periods of normal mental capacities intercalated with days of cloudiness of mind. Occasionally, such cognitive fluctuations may not be captured by a one-off assessment that focuses on mean-level cognitive performance. Recently, cognitive intraindividual variation (IIV) has attracted increased interest in the broader field of neurodegeneration because of its potential in predicting underlying CNS disorders and their progression. Cognitive IIV can be subdivided into inconsistency and dispersion. The former measures variations in cognitive performance across trials within a task or across sessions spanning longer intervals. The latter highlights variations across multiple tasks at a single point in time.

Cognitive IIV increases with age and cognitive decline in HIV-uninfected adults, as well as in those with neurodegenerative diseases including AD and PD. Moreover, it correlates with CSF biomarkers of AD. Cognitive IIV better detects mild cognitive impairment (MCI) and AD, and better predicts cognitive deterioration than mean-level cognitive performance. Structurally, cognitive IIV is correlated with WM integrity of the brain in older adults with or without AD. Cognitive IIV increases with concomitant impairments in attention, memory, and language in the older population, especially attentional lapses and fluctuations in executive control, suggesting that cognitive IIV can arise from interruptions of the grey and white frontal cortex neural network.[11] Given its anatomical proximity to the frontostriatal system compromised by HIV infection, people with HIV may demonstrate abnormal cognitive IIV.

Recent studies support this hypothesis. Cognitive dispersion and variability in accuracy response across trials increased with age and HIV status. Increased cognitive dispersion was associated with worse cognitive performance in a study that included both people with HIV and HIV-uninfected controls. Functionally, increased dispersion in people with HIV predicted worse medication adherence, subsequent dependence in activities of daily living, future cognitive decline, and death after controlling for HAND severity and global cognitive functioning. However, the relationship among cognitive IIV, global cognitive performance, and structural changes of the brain is less clear. In a cross-sectional study, total grey matter volume was inversely associated with cognitive dispersion but was independent of HIV status. In another longitudinal study, participants with HIV showed a greater dispersion than the HIV-uninfected controls despite similar global cognitive test performance. Furthermore, greater dispersion was related to lower fractional anisotropy values in the anterior thalamic radiations and the superior longitudinal fasciculus. Taken together, cognitive IIV appears to be a potential tool for HIV-related cognitive deficits and for age-related CI.

Current Guidelines and Recommendations for Cognitive Screening in HIV Infection

To date, evidence for and against routine cognitive screening in HIV infection remains inconclusive. The US Preventive Services Task Force (USPSTF) concludes that, among asymptomatic adults without HIV above 65 years old, screening for CI does not show clear evidence of benefit or harm to patients and their caregivers.[12] Although earlier detection and the subsequent intervention of CI could be beneficial to patients and their caregivers, the stress of cognitive screening, the risk of a false-positive result, and the stigma of CI should be carefully balanced. It is important to clarify that these screening recommendations relate to individuals without cognitive symptoms rather than a diagnostic workup that may typically occur among patients presenting with cognitive symptoms.

In the context of the varied cognitive impairment profile in HAND and the uncertain nature of the interaction between HIV infection and aging,

Table. Summary of Cognitive Screening Recommendations From Various Guidelines for People With HIV

British HIV Association (BHIVA)[14]	- All individuals with HIV should have regular screening to identify psychologic support needs - Individuals with HIV should have access to screening for cognitive difficulties within the first 3 months of receiving an HIV diagnosis
European AIDS Clinical Society (EACS)[16]	Clinicians can make use of a 3-question screening tool for people with HIV who present with cognitive complaints: 1. Do you experience frequent memory loss (eg, do you forget the occurrence of special events, even the more recent ones, such as appointments, etc)? 2. Do you feel that you are slower when reasoning, planning activities, or solving problems? 3. Do you have major difficulties paying attention (eg, to a conversation, book, or film)? Answering "yes" to 1 or more of these questions may suggest the presence of cognitive disorders, although not necessarily linked to HIV. Attending clinicians should consider referral to a neurologist and clinical psychologist for further assessment as appropriate
International Antiviral Society–USA (IAS–USA)[15]	Periodic assessment of cognitive function using a validated instrument is recommended for people with HIV who are older than 60 years of age
World Health Organization (WHO)[13]	Routine screening and management for mental health disorders (particularly depression and psychosocial stress) should be provided for people from key populations with HIV in order to optimize health outcomes and improve adherence to antiretroviral therapy

recommendations about cognitive screening are considerably different and nonspecific in HIV management guidelines (Table). For example, the World Health Organization (WHO)[13] and the British HIV Association (BHIVA)[14] recommend routine screening and management of mental health disorders for key populations of people with HIV to optimize health outcomes and ART adherence. However, the guidelines do not specify the preferred screening tools nor recommend a frequency of screening in asymptomatic people with HIV. Likewise, the IAS–USA guidelines suggest routine assessment of cognitive function every other year using a validated instrument in people with HIV after the age of 60 years, but it does not describe a validated instrument with good performance characteristics. The IAS–USA guidelines[15] note that individuals with progressively worsening symptoms of HAND should be referred to a neurologist for evaluation or to a neuropsychologist for formal neurocognitive testing.

Contrary to the aforementioned guidelines, the European AIDS Clinical Society (EACS) recommends a stepwise approach in tackling cognitive complaints in people with HIV. The EACS v10.0 guidelines[16] recommend evaluating cognitive complaints in people with HIV using a 3-question screen that covers memory loss, mental slowing, and attention difficulties. Positive response in any 1 of the 3 questions warrants further evaluation and referral to a neurologist and neuropsychologist. In a study with mandatory application of the 3-question screen to 974 mostly viral-suppressed people with HIV, around one-fourth of them answered positively to at least 1 of the 3 questions. Among those, half showed CI in formal neuropsychological assessment. The positive and negative predictive values of genuine CI by this approach were 0.35 and 0.7, respectively. Individuals who responded positively to all 3 questions showed an increased risk of underlying depression. Although the EACS approach does not offer satisfactory predictive value to cognitive complaints in people with HIV, it is practical and clinically pragmatic in tackling a mix of neuropsychiatric symptoms in people with HIV and is especially useful in resource-limited settings.

Available Tools for Cognitive Screening in Aging People With HIV and Cognitive Complaints

Although full neuropsychologic assessment remains the gold standard for diagnosing HAND, it is not readily available in most clinical settings and can be too cumbersome for use in screening. Simple screening tools such as the HIV Dementia Scale (HDS) and the International HIV Dementia Scale (IHDS) have been developed for the detection of the most severe forms of impairment in resource-limited settings. However, their usefulness in the ART era, especially their accuracy in detecting milder forms of HAND, is poor. Based on the recommended cutoff score, HDS is not sensitive to CI in people with HIV on suppressive ART, with a sensitivity and specificity of 24% and 92%, respectively, in the CHARTER cohort. Modifying the raw cutoff score to 14 yielded better sensitivity and specificity of 66% and 61%, respectively.

Similar performance characteristics are noted for the IHDS in the ART era. In the initial validation study, the IHDS demonstrated sensitivity and specificity of 80% and 57%, respectively, in the US cohort, and 80% and 55%, respectively, in the Uganda cohort in identifying HAD. However, in 2 subsequent Africa-based studies, despite around two-thirds of the participants being on ART, 64% and 83% were screened positive by the IHDS, highlighting the likely overestimation of HAD. Moreover, 77% of the HIV-uninfected controls in one of the studies would have been rated as "cognitively impaired" based on a cutoff score of 10 in the IHDS.[17] This figure is well above the reported HAD prevalence of 25% to 31% in Uganda and South Africa using conventional neuropsychologic testing. In a Dutch study with mostly treated people with HIV, combining the IHDS with the EACS 3-question screen showed sensitivity and specificity of 50% and 73%, respectively.

The Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA), the latter of which has been translated and validated in different languages, are commonly used cognitive screening tools to identify age-related CI in HIV-uninfected adults. MMSE is the most widely used screening tool for AD, but it is not sensitive enough to detect MCI. Without testing executive function and motor skills, MMSE is insensitive to HAND. MoCA evaluates visuospatial/executive, naming, memory, attention, language, abstraction, delayed recall, and orientation function in an individual; thus, it is potentially useful for aging people with HIV who present with CI driven by HAND, AD, vascular CI, or in combinations. In a study that identified HAND in people with HIV older than 60 years of age, MoCA with an optimized cutoff score of 25/30 or less showed sensitivity and specificity of 72% and 67%, respectively. In a meta-analysis that included 8 cross-sectional studies using MoCA to identify HAND, the authors concluded that a lower threshold than the original cutoff (≤25/30) of MoCA would lower false-positive rates and improve its diagnostic accuracy, but the choice of cutoff always comes with a sensitivity–specificity trade-off.[18]

With the advancement of portable digital devices and their increased penetration into daily activities, including among the elderly, digital cognitive assessment could be a solution to replace conventional neurocognitive assessment, which is labor-intensive and highly skill-dependent. More recently, digital cognitive assessments are being developed as mobile applications (apps) operated on tablets with or without an internet connection. Compared with computer-based assessment, mobile apps operated on tablets offer a better-standardized testing environment, including screen size and output recording using a touchscreen that is timed and scored automatically. With standard in-app instructions, digital cognitive assessments allow the possibility of operation outside the clinic with or without supervision. With careful selection of test modules and cutoff

scores, digital cognitive assessments have demonstrated their usefulness in detecting preclinical AD.[19] NeuroScreen and Cogstate have been tested for validity in detecting HAND in people with HIV, and both showed reasonable sensitivity and specificity in identifying CI in symptomatic and asymptomatic people with HIV. Future research should explore the use of digital cognitive assessments for cognitive screening and assessment.

Prevention of Cognitive Impairment in Older People With HIV

To date, a number of ART modification theories to improve HAND have been studied, including the application of CNS penetration effectiveness and monocyte efficacy as well as ART intensification by adding an integrase strand transfer inhibitor and maraviroc, a CCR5 antagonist, to the standard 3-drug ART regimen. Nevertheless, there is considerable enthusiasm toward ART simplification to reduce ART-related toxicity. Such an approach could be especially important to older people with HIV at an increased risk of organ failure. The CNS outcomes of these ART modifications were recently reviewed by Handoko and collegues.[20] However, whether proactive adoption of these strategies is beneficial to long-term cognitive stability in asymptomatic people with HIV has not been examined in large-scale studies. In general, modification of ART is not recommended except in the case of symptomatic CSF viral escape, during which clinicians should revise the ART regimen according to the viral resistance profile in the CSF.

Meanwhile, general measures to delay the onset of dementia in HIV-uninfected populations are also essential in HIV care. A recent review of dementia in individuals without HIV pinpoints the importance of modifiable risk factors, including the treatment of hypertension, diabetes, obesity, hearing impairment, and depression, as well as smoking cessation, encouraging physical and social activity, decreasing alcohol consumption, and avoiding traumatic brain injury.[21] The reviewers estimated that these modifiable risk factors could account for up to 40% of dementia worldwide, compared with an estimated AD risk of 7% in those bearing the *apolipoprotein E4* gene. Indeed, an intensified management of these modifiable risk factors is especially important as they are highly prevalent in people with HIV compared with HIV-uninfected populations.

Conclusion

Despite the improved understanding of neuroHIV, a knowledge gap exists concerning CI in aging people with HIV. Systemic and cerebral inflammation persists, albeit to a lesser extent, in people with HIV after suppressive ART. Current evidence supports that persistent immune activation could facilitate both systemic and cerebral age-related noncommunicable diseases. In the CNS, people with HIV may experience premature aging and accelerated cognitive aging. However, the characteristics of CI in older people with HIV remain less clear, particularly the involved cognitive domains and the speed of progression. Intensified atherosclerosis could make vascular cognitive impairment a predominant component in older people with HIV. The CI of people with HIV may present with fluctuations of cognitive performance that are occasionally overlooked by a one-off cognitive assessment. Moreover, screening tools such as the HDS and IHDS, developed for more severe forms of HAND, are generally insensitive to milder forms of HAND and are unlikely useful in detecting age-related CI. Current HIV management guidelines have diverse recommendations for cognitive screening in older people with HIV, as well as the frequency and the recommended tools. Digital cognitive assessments with reasonable sensitivity to CI allow repeated testing and automatic collection of test performance. They might serve as useful screening tools and potentially fill the gap of unrecognized cognitive fluctuations. Although clinicians treating people with HIV should tailor their services for cognitive symptoms, based on the available resources, priority should be allocated to management of modifiable risk factors of dementia as these factors also impact the prognosis of other age-related noncommunicable diseases.

This article was based, in part, on a webcast presented by Dr Valcour in June 2021: https://youtu.be/oehfwLloBZI. This article was prepared by Dr Chan and Dr Valcour in October 2021.

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For additional reading and resources, click here.

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Perspective

Addressing the Challenges of Vaccine Hesitancy Broadly and Related to COVID-19 Vaccines

Vaccine hesitancy is one of the greatest health care challenges of our time, as recently highlighted by the experience with COVID-19 vaccines. It is now clear that several current COVID-19 vaccines are highly effective in preventing severe disease, hospitalization, and death from the disease, but their effectiveness has been greatly undermined by the many unfounded conspiracy theories, active disinformation, and fears (real or imagined) circulating through social media and through society in general, persuading millions of people worldwide not to receive the vaccine. Fortunately, there are numerous practical strategies that physicians and other health care professionals can employ in communicating effectively with vaccine-hesitant individuals, including using humble inquiry, compassionate listening, and storytelling, as well as engaging the entire health care team in providing accurate information. This article summarizes the major points of an IAS–USA-sponsored webinar held on August 3, 2021, titled COVID-19 Vaccine Hesitancy, Crucial Conversations, and Effective Messaging for Patients and Health Care Teams *by Marie T. Brown, MD, an expert on adult immunization. The webinar was moderated by Constance A. Benson, MD.*

Keywords: COVID-19, vaccine hesitancy, SARS-CoV-2

Last year, a pregnant woman in her second trimester approached one of her physicians and expressed apprehension about receiving the COVID-19 vaccine. She believed in the benefits of the vaccine but was concerned by a lack of data supporting its safety for a fetus, as such data was not yet available in early 2021. The doctor immediately put her at ease. He agreed that there was no published data guaranteeing the safety of the vaccine for pregnant women, but he confirmed that there were tragic examples of pregnant women who did not survive COVID-19 disease. He shared that the obstetricians with whom he worked and the nurses on his staff who were pregnant had all received the vaccine and had no problems.

The doctor told the woman that any potential negative side effects of the vaccine were far, far outweighed by the well-known risks to pregnant women of contracting COVID-19, including pregnancy loss, preterm delivery, poor pregnancy outcomes, extended newborn intensive care unit stays, and more. The doctor also mentioned that his wife had recently received the vaccine and done just fine. The doctor made the woman feel smart for getting vaccinated in her second trimester.

With that confidence, the woman had no further hesitation and was vaccinated. She gave birth to a healthy baby a few months later. After the birth, she and her family were comforted to know that her newborn child now had some passive antibodies and was already somewhat protected against the disease. Months later, she brought the same confidence to her booster-shot appointment while breastfeeding her 5-month-old infant.

This true story was shared (with the new mother's permission) by adult vaccination expert Dr Marie Brown during a recent IAS–USA webinar titled *COVID-19 Vaccine Hesitancy, Crucial Conversations, and Effective Messaging for Patients and Health Care Teams*. The woman in the story? Dr Brown's daughter.

This experience is an example of one way physicians and health care professionals can address vaccine hesitancy with their patients: by telling stories. For many vaccine-hesitant patients, hearing a story like this from their personal physician is more powerful than facts and statistics. Other important tools that doctors can employ include engaging the entire health care team in the provaccine message, humbly inquiring into patients' fears, compassionately listening to patients' concerns, and avoiding hostility or frustration when presented with misinformation or conspiracy theories.

Physicians are in a uniquely advantageous position in the fight against vaccine hesitancy. According to one study, the most influential voice in whether a vaccine-hesitant individual decides to receive the COVID-19 vaccine is not national, state, or local health organizations, but rather that individual's personal physician or health care practitioner (Figure 1).[1] It is incumbent on physicians, their teams, and other medical personnel to be on the same page in how they address this crucial public health issue.

Vaccine hesitancy, social media misinformation, and active disinformation have emerged as some of the greatest health care challenges of this generation. Still, not all the news is dire. Based on surveys conducted during the spring of 2021, about 50% of the wait-and-see group (those individuals who have considered getting the COVID-19 vaccine but who are "waiting to see" its long-term effects) stated that they would strongly consider taking the vaccine once it was fully approved by the US Food and Drug Administration (FDA),[2]

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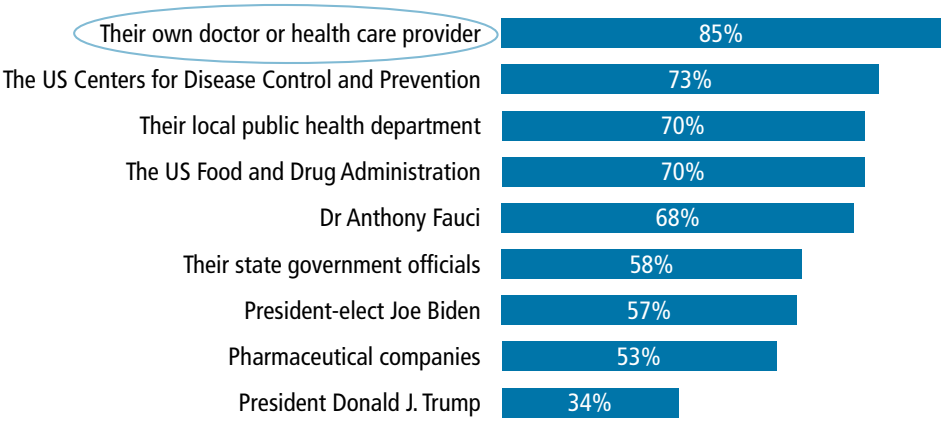

Figure 1. Percentage of Americans in December 2020 who said they had a great deal or a fair amount of trust in each of the presented options to provide reliable information about the COVID-19 vaccine. Adapted from the Kaiser Family Foundation.[1]

and on August 24, 2021, the Pfizer vaccine was the first to receive full FDA approval. The United States also recently passed an important milestone: At the time of the webinar, over 50% of those who were in the wait-and-see group in January 2021 had received at least one dose of the vaccine.[3] This is encouraging news. However, with only a bit over 70% of eligible Americans having taken at least one dose of the COVID-19 vaccine at this time, there is still much more work to be done and many more difficult conversations to be had with vaccine-hesitant patients.

For many physicians and for others with scientific backgrounds, the knee-jerk reaction when speaking with vaccine-hesitant individuals can often be to confront mistakes and misinformation with cold hard facts. At this point, such an approach is not practical if our goal truly is to convince as many people as possible to choose to be vaccinated. Instead, health care professionals can explore using a host of other communication techniques, such as telling stories, making those stories personal, responding with empathy to people's objections to vaccines and then easing the conversation compassionately in more productive directions, tailoring your message to each patient's concerns, and engaging the entire medical team in provaccine messaging. These are all more practical tactics and much more likely to guide patients in the right direction.

The Roots of Vaccine Hesitancy and the Social Media "Infodemic"

Propaganda, fearmongering, conspiracy theories, and disinformation are likely as old as human society itself. Throughout history, many causes and culprits have coerced large segments of various societies into believing many things that simply are not true, often to highly detrimental ends. Vaccine hesitancy can be seen as just another chapter in that lamentable, ongoing narrative.

Interestingly, though quite discouragingly, modern vaccine hesitancy has its earliest roots in the work of various medical professionals. Large segments of the public readily accepting their dubious claims is disconcerting, but not necessarily surprising. Public confidence in governmental and corporate institutions has never been sacrosanct, often for very good reason. Add to this the American medical industry's more than lamentable historical record; the impact of the long-running Tuskegee Syphilis Study,[4] sponsored by the US Public Health Service, and the Puerto Rico Pill Trials[5] on communities of color are just 2 of many examples of industrial and governmental malfeasance contributing to public mistrust of the medical establishment.

Sadly, this mistrust, as well as perhaps the notorious shortness of human memory, has led many people to forget one incontestable truth: Second perhaps only to sanitized drinking water, vaccines are arguably the most successful public health achievement in the history of mankind. This statement is not hyperbole. It would be impossible to quantify the number of lives saved and the overall worldwide improvement to quality of life due to, for example, the smallpox, measles, and polio vaccines alone. However, as the hackneyed-but-true expression goes, "Those who cannot remember the past are condemned to repeat it." Measles was virtually eliminated from the United States decades ago, but in recent years it has seen a resurgence,[6] largely due to American parents opting not to vaccinate their children. Polio is poised to make a similar comeback in other parts of the world.[7]

How have we gotten here? There are many, many answers to that question, but one of the most obvious is the influence on American and worldwide culture of the Internet and social media, which have offered the fertile soil in which the antivaccine movement has taken root and flourished. A casual glance at the statistics is startling. Antivaccine tweets are twice as likely to be retweeted as provaccine tweets, and 4 times more likely than neutral tweets.[8] One report shows social media platforms realizing $1 billion in annual revenue from antivaccine content alone,[9] giving the corporations who own those platforms very little profit motive to stem the antivaccine tide. Another study suggests that if current trends continue, the antivaccine movement could eventually overwhelm provaccine voices online, because antivaxxers are heavily entangled with the very large online presence of undecided (or wait-and-see) individuals, and provaccine voices online remain more peripheral, preferring to communicate only with each other (Figure 2).[10] Clearly, the online antivaccine movement is entrenched, integrated, and growing stronger every day.

This can be difficult to understand, because by any measure there are actually many more provaccine people in America than antivaccine people.[10] That does not even take into account the millions of wait-and-see individuals

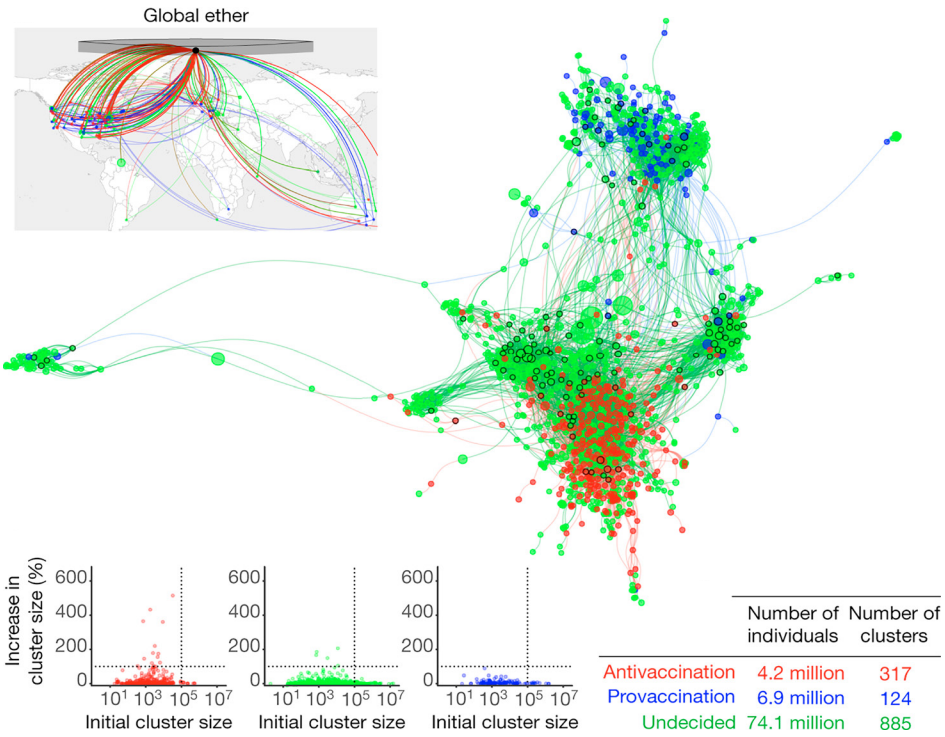

Figure 2. Entanglement of antivaccine and provaccine advocates with undecided individuals on social media. Antivaccine clusters (red) overlap with a larger number of undecided clusters (green) than do provaccine clusters (blue), indicating the powerful, entrenched reach of antivaccine messaging online. Adapted from Johnson et al.[10]

who have already chosen to get the COVID-19 vaccine. Clearly, anti-vaxxers are the minority. However, the Internet and social media (and sometimes the mainstream media) allow small groups of people who hold extreme beliefs but have outsized voices to appear more mainstream, not to mention that the antivaccine movement's highly emotional, anecdotal approach to producing content is very effective on social media, and that the provaccine movement's messaging has floundered at almost every point. Because of this, the antivaccine movement has enjoyed great success online, resulting in what the World Health Organization (WHO) has called an "infodemic," a rapid, toxic spread online of false information about COVID-19 and the COVID-19 vaccine.[9]

This infodemic, and the conspiracy theories and misinformation found therein, is wide-ranging in scope. For example, the "plandemic" narrative proposes a decades-long conspiracy between global governments, pharmaceutical companies, the Centers for Disease Control and Prevention (CDC), Google, and other powerful entities to engineer and release COVID-19 for sheer profit-motive purposes.[11] Another popular conspiracy theory involves 5G cell phone signals activating microchips embedded in the COVID-19 vaccine to track, and perhaps control, the vaccinated; an early version of this conspiracy even led to the literal burning of 5G phone towers in England in 2020.[12] Some anti-vaxxers claim that vaccines were invented to depopulate the Earth or to target certain ethnic or racial groups. The list goes on and on.

Other COVID-19 vaccine myths may seem more "science-based" (and thus more persuasive) at first glance, but they quickly turn out to be equally invalid: that you can catch COVID-19 from taking the COVID-19 vaccine, that COVID-19 vaccines contain fetal cells, that COVID-19 vaccines have been shown to cause infertility, and that COVID-19 vaccines can change your DNA. It is easy for physicians and scientists to dismiss these obviously false myths out of hand. However, all patient-facing medical personnel would do well to at least familiarize themselves with these myths, if only to be prepared when vaccine-hesitant individuals offer them as explanations for their fears.

Though myths abound regarding COVID-19, one thing that is not under debate is that COVID-19 vaccine hesitancy in the United States falls along predictable political and socioeconomic lines: Those in the "definitely not" group are overwhelming Republican, White, and live in rural settings, and those in the "already vaccinated" group are overwhelmingly Democratic and college educated. However, a deeper dive into the numbers reveals some important trends. For example, a large percentage of the wait-and-see group is made up of Black and Hispanic individuals, as well as 18- to 29-year-olds, and the definitely-not group, those who have stated they will never get the COVID-19 vaccine (or any other vaccine) under any circumstances, seems fixed at 15% of the American population, and has been historically fixed at that level since well before COVID-19.

It stands to reason that focusing provaccine messaging on the definitely-not group would not be very fruitful, because they are not likely to be swayed in any case. Instead, the medical establishment can shift its full messaging focus to the very large wait-and-see groups, in the hopes of convincing as many of those individuals as possible to move from being vaccine hesitant to fully vaccinated.

Engaging With Patients

How can that be accomplished? If it is more effective to focus provaccine efforts on vaccine-hesitant (wait-and-see) individuals, what tactics are most useful? Put more simply, how can physicians and medical professionals educate ourselves to communicate more effectively with vaccine-hesitant patients than we have so far?

It should be abundantly clear by now that at least one approach will never work: accosting vaccine-hesitant patients with reams of data, no matter

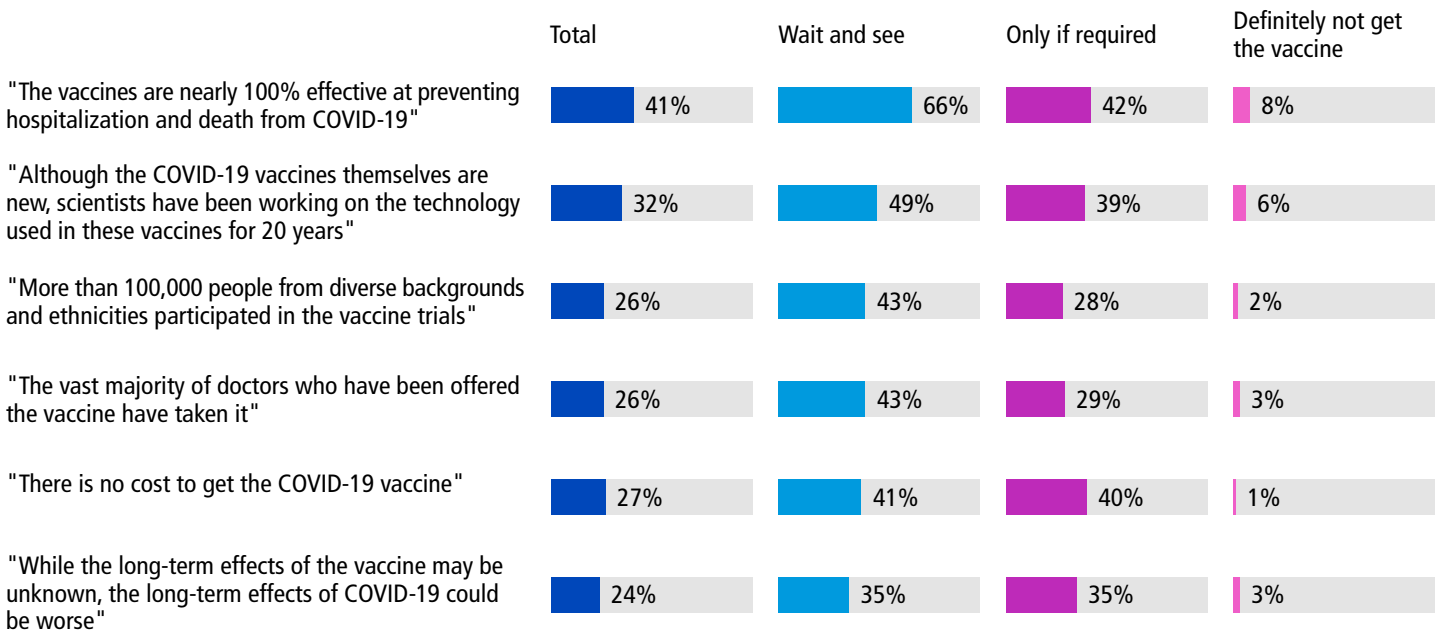

Figure 3. Percentage of Americans in March 2021 who said they were most likely to get the COVID-19 vaccine if they heard each of the following messages. Adapted from the Kaiser Family Foundation.[13]

how scientifically accurate those data are. However, some fact-based messages do appear to be more effective than others (Figure 3).[13] For example, studies have shown that vaccine-hesitant patients are much more likely to opt for the vaccine when they learn that (1) the vaccines are nearly 100% effective at preventing hospitalization and death from COVID-19, or that (2) the technology used to develop the COVID-19 vaccines is not brand new, as seems to be widely believed, but has in fact been in development for nearly 20 years. Patients also seem to respond very strongly when physicians talk about the vaccine helping prevent their loved ones from getting sick.[1] Physicians and medical personnel can familiarize themselves with these simple, impactful messages, because doing so goes a long way toward preparing for these difficult conversations.

One of the most powerful tools for engaging with vaccine-hesitant patients is storytelling. Storytelling is hardwired into every human culture and every human brain, so narratives, anecdotes, and metaphors can be very effective ways of breaking down barriers and transmitting life-saving information. Telling emotionally engaging stories is not necessarily a natural skill for many physicians and scientists, but in the current cultural environment, it is a very important skill to foster. With this in mind, think about your own professional and personal experience with COVID-19. Has someone in your family been impacted by the disease? Have you had patients who took the vaccine and had positive outcomes, or patients who did not take the vaccine and had negative outcomes? How did those events affect you personally, make you feel? The more details and emotions you can provide to bring the story to life (while of course maintaining patient privacy), the more effective your message can be. If you know other medical professionals who seem more naturally gifted at telling stories, don't be hesitant to ask them for advice. Often, telling a good story is as simple as remembering a few key bullet points of a narrative, then practicing a few times until telling the story becomes natural.

Another valuable approach involves engaging the entire health care team, not just physicians, in provaccine messaging. Although nearly all practicing physicians in America have chosen to be vaccinated, 3 in 10 health care workers had not been vaccinated for COVID-19 as of March 19, 2021, and 18% of health care workers had not planned to get vaccinated at all.[14] This massive disparity within the health care ranks makes it difficult to form a unified front in the messaging battle against COVID-19 vaccine hesitancy; an opportunity is lost every time a patient interacts with a health care worker, including nurses, medical assistants, front desk employees, and many others, and that patient is not addressed about receiving the vaccine. It is crucial to engage with all health care workers on a given team, not only to encourage them to be vaccinated for their own benefit, and not only because they might encourage patients to do the same, but also because those workers can become trusted resources of information about what is happening in the community. Put another way, it is likely much easier to change your team's beliefs than your patients', and the more you do so, the more effective your entire team's unified efforts will be.

Other important advocates to engage with are provaccine community leaders. These can include local celebrities, religious leaders, business leaders, and politicians (although in our current environment, some politicians are the source rather than the solution for vaccine hesitancy). Dr Brown met years

ago with the pastor of a large Black church in Chicago, where she practiced internal medicine. During this meeting, the pastor shared with Dr Brown that he had just had a new grandson. This led Dr Brown to inquire if the pastor's tetanus, diphtheria, and pertussis (Tdap)/whooping cough vaccination was up to date. Then, just as the pastor was about to leave the room, he mentioned that his church baptizes more than 10 babies per week, and he asked Dr Brown if his deacons should all get the Tdap vaccine as well. Dr Brown, of course, said yes. "Because he encouraged his deacons, who would have been holding these newborns, and then having an opportunity to talk to their parents, he probably decreased the pertussis rate on the West Side of Chicago singlehandedly," Dr Brown said.

Even with the help of community advocates and the health care team, physicians will still need to meet directly with vaccine-hesitant patients. Fortunately, numerous websites and online toolkits are available to help prepare medical professionals for these conversations. The free American Medical Association (AMA) STEPS Forward™ toolkit offers useful case studies that walk physicians through various vaccine-related conversations, as well as many patient objections you might encounter.[15] Other toolkits aim to help physicians talk with patients, including Black and Latinx patients, about the realities of COVID-19 and the vaccine, as well as providing advice for effective social media use with those communities.[16] For some health care organizations, it might also be worth using a physician belief scale to measure you and your team's beliefs about the psychosocial aspects of patient care, which can determine whether you even believe that addressing a patient's personal thoughts or opinions is valuable.[17] Using such a tool can offer advice on how to change that mindset for the better.

Another crucial aspect of mindset to consider is your answer (and your patient's answers) to the following question: Do you believe getting the COVID-19 vaccine is a social responsibility, or is it solely a matter of personal choice? Most people on the provaccine side believe the former to be true. However, research shows that the American population is split down the middle on this question.[1] Because of this, physicians risk alienating nearly 50% of the population if they push a narrative to vaccine-hesitant patients that they, the patient, have a responsibility to protect others by getting the vaccine, which could conflict with those patients' strong belief in their own personal choice. When interacting with vaccine-hesitant individuals directly, it is not necessary to agree with them on this issue, but it is crucial to respect their beliefs, and not to impose one's own belief system upon them.

Similarly, it is vitally important, when speaking with a vaccine-hesitant patient, not to repeat out loud the myth or conspiracy theory they might have offered you as their reason for not getting vaccinated. Simply hearing the myth spoken out loud, even if the medical professional is debunking it, can in fact reinforce the myth. A better tactic is to genuinely acknowledge that the vaccine-hesitant individual seems invested in learning as much as possible to ensure their own health and the health of others, and then to guide the conversation toward your practical, medically informed advice on how to do that.

On this and many other potential points of disagreement with vaccine-hesitant patients, physicians must do everything in their power to always remain calm and composed, and to allow patients to fully explain their point of view, no matter how much the physician might want to immediately correct them. For example, a patient might ask your opinion of hydroxychloroquine. As a physician with extensive scientific training, you are likely to have very strong opinions about hydroxychloroquine. However, it is not advisable to offer those opinions immediately, and certainly not advisable to offer those opinions in frustration or anger. Instead, a more effective response is to say something with a positive spin, such as: "Oh, I see

Figure 4. COVID-19 vaccine pins can help support a provaccine environment.

that you are sincerely worried about this disease, and you are looking for something that will be effective in helping you prevent infection. Is that right?" That type of response opens a conversational door rather than closing it. Although a lengthy conversation will probably take time out of a physician's busy schedule, keeping the patient positively engaged is much more likely to move them toward understanding the incredible benefits of the COVID-19 vaccine.

Other, seemingly more simplistic interventions can also be very effective. Wearing an "I got my COVID shot" button or other similar paraphernalia, and having as many members of the medical team as possible do so as well, sends a clear, unified message to vaccine-hesitant patients (Figure 4). When talking with patients who might claim religious or political reasons for not taking the COVID-19 vaccine, do not be afraid to use your phone to show them online articles from websites they might already use regularly: for example, the 2021 *Fox News* article[18] where former President Donald Trump urged all Americans to get the vaccine and stated that the vaccine is safe and effective, or other stories about how Reverend Franklin Graham and Pope Francis are both publicly in favor of Christians getting the COVID-19 vaccine. Physicians should tailor this approach to the individual patient, and ask first if the patient would like to view some of these news stories. Agreeing

to look at these sources of information together could be an effective first step in overcoming their hesitance.

Finally, the core of any approach to dealing with vaccine-hesitant patients must be humble inquiry. Humble inquiry means sitting down with patients, taking time, asking them sincere questions, listening to them, acknowledging their points of view calmly and compassionately even when one does not agree, and then doing one's best to tailor the most helpful message directly to them. Most people can tell the difference between someone reading from a script and someone really trying to connect emotionally and empathetically. Like storytelling, humble inquiry is not a natural skill for all people, but it is a skill that can be learned and fostered. In this vital struggle against COVID-19 and vaccine hesitancy, we should all consider doing so.

Q&A Session

After the discussion around the numerous tactics for addressing vaccine hesitancy with patients, Dr Brown and Dr Benson engaged in a Question and Answer session with the webinar participants. Following is an abridged transcript of that conversation, edited for brevity and clarity. Again, these discussions were based on the current knowledge as of August 3, 2021, the presentation date of the webinar.

Question:

How can we best address vaccine hesitancy in light of the study in Massachusetts showing that more than 70% of those in the July 2021 outbreak there were people who had been vaccinated? How would you approach the messaging?

Dr Benson:

A lot of the messaging around COVID-19 vaccines has been confusing, largely because the media and even many of our colleagues have not made the distinction between being infected and able to transmit the infection, versus having severe disease, being hospitalized, or having a high risk of dying. The vaccines that are available to us right now are extremely effective in preventing severe disease, preventing hospitalizations, and preventing deaths.

In our experience in San Diego, of those individuals hospitalized for COVID-19, more than 80% are people who were not vaccinated at all, and the remainder are partially vaccinated or have underlying conditions that interfered with a robust immune response to the vaccine. However, the majority of those hospitalized who had been vaccinated have not required admission to the intensive care unit (ICU). More than 50% of the cases in certain areas and more than 90% in other areas experiencing large surges are with the Delta variant, and although fully vaccinated individuals can be infected with the Delta variant, they are not developing severe disease. With the outbreak of COVID-19 infection in Massachusetts, the majority of individuals had no or mild symptoms and were not hospitalized.

These infections, in fact, are an advertisement for how effective the vaccines are in preventing the majority of those people from getting sick and from being hospitalized and from dying.

Question:

Dr Brown, how did you convince your daughter, who was in the second trimester of pregnancy, to get vaccinated? And as a corollary to that, how do you encourage breastfeeding parents to be vaccinated?

Dr Brown:

That's a great question. I did not need to convince my daughter, who is not in health care but believes strongly in science. She asked her physician, who said, "Get the vaccine. My wife and our staff got it to keep themselves and others healthy." Understanding that the breast milk may be protective for the newborn, she actually got her third dose while still breastfeeding and feels comforted that she provided the best protection for her baby. Her physician used an anecdote, and that's all she needed. So, it was a trusted person who was caring for her sharing a personal and clear message.

Question:

Why are we calling this "vaccine hesitancy" when people are refusing to be vaccinated? Hesitancy makes it seem like they're not sure if they want the vaccine.

Dr Brown:

In my opinion, "hesitancy" is a good term, because we want to (and often can) move vaccine-hesitant people to vaccine-accepting people. The 10% to 15% of people who refuse the vaccine will always refuse the vaccine. Even back in the smallpox era, the term "conscientious objector" was coined for people who refused to take the smallpox vaccine in London hundreds of years ago. We are not going to change the proportion of those who refuse; it has been consistent throughout history.

What we need to focus on is the vast majority who are hesitant. They want to do the right thing. They need a trusted person to be knowledgeable, to respect their concerns, and to answer their questions.

Question:

How likely are unvaccinated individuals to get infected with SARS-CoV-2? Will 100% of unvaccinated people get COVID-19 if they do not get vaccinated?

Dr Benson:

The answer depends on the level of risk of the person and with whom they are in contact. The current circulating Delta variant is tremendously transmissible. (Update: The Omicron variant is even more transmissible than the Delta variant.) People carrying the Delta (and now Omicron) variant have such high viral loads in the nasal secretions that someone coming into close contact with them in an indoor setting has a high likelihood of becoming infected if they're not vaccinated.

For people who have been vaccinated, however, we do know that breakthrough infections are common, although marginally less common than

among those who are unvaccinated. We do know that people at high risk, those who are immunocompromised, for example undergoing cancer chemotherapy or transplant recipients, those who are over the age of 65 years, or who have other underlying conditions that affect immune function may not have as robust an immune response to any vaccine, and may be at some higher risk of infection and of more serious disease.

The point here is not that 100% of people who are fully vaccinated will be protected from infection by the Delta variant, but that the risk of infection may be lower, and the risk of serious disease, hospitalization, and death is substantially lower than for those not vaccinated at all.

Question:

Please address the myth circulating in the media and as stated by a former Nobel laureate that people who have received COVID-19 vaccines would die within 2 years as a result of antibody-dependent enhancement.

Dr Benson:

Antibody-dependent enhancement after vaccination was a very early concern of the scientific community when coronavirus vaccines were first investigated. Some of that was related to (1) the experience with very early coronavirus vaccines in veterinary practices, where animals developed antibody-dependent enhancement and actually got sicker after encountering coronavirus postvaccination; and (2) the experience with dengue vaccine development, which has been hampered by similar antibody-dependent enhancement.

The scientific community has been monitoring this closely since the origin of the first severe acute respiratory syndrome (SARS), SARS-CoV, and Middle East respiratory syndrome (MERS) outbreaks. There is no evidence in any of the human studies with those viruses, or from the data that emerged from the SARS-CoV-2 vaccine trials, that antibody-dependent enhancement has occurred. There has not been a single case reported out of the many millions of people who have now been vaccinated. Thus, there is no evidence that it would occur 2 years after vaccination.

Can we say that with absolute certainty? In my opinion, yes.

Question:

How do you address questions from patients with no absolute answer? How do you address that kind of conversation?

Dr Brown:

I think it is important to pivot quickly to what we do know. If we are trying to get somebody to stop smoking, telling them what bad things can happen, like emphysema or lung cancer, is less effective than highlighting good things, such as being able to play with their grandkids. To encourage vaccination, highlighting its benefits is effective. Do you want to get back to work? Do you want your kids to get out of the house and go back to school? Do you want to be able to hug your parents and see your brothers and sisters? What are you missing now? Maybe they've lost their job.

Pivoting quickly to the benefits of getting the vaccine: It is so safe relative to disease. For example, compare polio and measles vaccination with the encephalitis-associated brain damage that can occur with disease. Share details of the last patient you saw with COVID, without compromising patient confidentiality, to make it more relevant to your patient. Tell them they were a school teacher or a neighbor, whatever the experience was, and how vaccination could have saved them and their family heartache. Make it personal.

The people watching this webinar know the most heart-wrenching story of somebody who died of COVID-19, someone who lost their mother, their sister, or their wife. Share that story. Tell the heart-wrenching story about somebody who could have prevented their death had the vaccine been available. Note how fortunate we are now to have the vaccine. That's how I answer it.

Question:

We get lots of questions about COVID-19 and infertility. How do we respond to that?

Dr Benson:

This is a question that has generally been asked by pregnant women or women anticipating becoming pregnant who are worried about their own fertility. However, there is very strong evidence that with the overexpression of the receptors for coronaviruses in testes, it is far more likely that male infertility will be a complication of COVID disease, not of vaccination. People who get COVID, even if they don't have severe disease, have the potential for SARS-CoV-2 in the testes to decrease sperm count, decrease semen quality, and lower volume. Studies demonstrating short-term infertility in men who have recovered from COVID disease have been published. However, there are no data linking SARS-CoV-2 vaccines to any impact on the male or female reproductive systems or infertility in animal models postvaccination.

All of the infertility data related to COVID stem from this as a complication of COVID itself, not of the vaccines.

Dr Brown:

We should remember that mumps can cause orchitis and infertility, which would make sense to somebody. I think that's a really good message.

Question:

How effective are the current vaccines against variants, and will we need boosters? How durable is the vaccine protection?

Dr Benson:

What we can say, based on our current information, is that each of the vaccines are very effective against the current variants circulating at the time of this webinar in preventing severe disease, preventing hospitalization, and preventing death. We have learned from the experience with the Delta variant that they are not as effective in preventing people who are fully vaccinated from getting infected. There is still the potential with the Delta variant, although maybe not as high a potential as for the unvaccinated, that they could be infected and transmit to

another person. (Update: Our understanding with the Omicron variant is that it is even more highly transmissible than the Delta variant, vaccine efficacy in preventing infection among the fully vaccinated is lower, and breakthrough infections are occurring; however, rates of severe disease, hospitalizations, and deaths are lower among those fully vaccinated, and especially among those who have received a booster dose of a vaccine.) This is where we are with understanding vaccine efficacy.

With regard to vaccine boosters, the data from published studies and the messaging from the CDC is that there is a waning of the neutralizing antibody response over time, particularly after 6 to 9 months among those fully vaccinated. For most people with normal immune function, there is still sufficient neutralizing antibody and antibody-mediated cellular immunity to prevent severe disease, hospitalizations, and death at least following exposure to the Delta variant. (Update: A booster dose also further enhances that effect for the Omicron variant.)

However, our current data indicate there are vulnerable populations within the fully vaccinated, such as individuals who are immunosuppressed and individuals who are over 65 years of age. These individuals may have had a less robust early response or a more rapid waning of immunity than what we see in younger, healthier individuals.

(Update: As further data have accumulated, public health officials, the FDA, and the CDC are now in agreement that eligible adults and adolescents who have been previously vaccinated should receive a booster dose of vaccine 5 to 6 months following their initial vaccination. I think we're going to see recommendations from public health officials in the very near future that additional vaccine boosters will be necessary, perhaps every year, as we do with influenza vaccines. Whether it will be necessary to alter or adjust the current vaccines to accommodate current or new variants in the future remains to be established.)

Question:

Is it safe to mix different vaccines?

Dr Benson:

Based on current evidence, the answer is yes. Some countries, like the United Kingdom and Israel, began doing this early on even with the second vaccine dose, particularly when supplies were limited for certain types of vaccines. For example, the adenovirus vector vaccines are now being boosted with the mRNA vaccines in many countries. This appears to be safe in clinical trials, and has been endorsed by the CDC in the United States.

Question:

Do you have particular messages for talking about vaccine hesitancy among your Black or Hispanic populations? Are there tailored messages that you have advice about for those populations?

Dr Brown:

The website I showed, La Conversación,[16] has celebrities and trustworthy sources that address some of those concerns. We need to come prepared to these conversations about historical events like the Tuskegee Syphilis Study. We should approach all communities with humility and awareness that, for example, the Tuskegee Study was funded by the US government.

Dr Benson:

You made some very good points about some of the church leaders in African American communities. Making use of representatives of the community is a particularly important message, trying to have a champion, if you will, of vaccination.

There have also been a number of celebrities who can have tremendous influence over Black and Hispanic communities who have had a real hands-off approach to the issue of vaccina tion. In some instances, this has been misinterpreted as a lack of support for vaccination; however, searching for other celebrity champions more willing to tell their own stories has resulted in some of those messages starting to get out more effectively with people who listen to them.

Dr Brown:

Another myth that has arisen is around documentation required to get the vaccine. Undocumented people hesitate to access a government site that requires documentation, such as a government state-issued ID or social security number. This is where access for the vaccine hesitant is important. Having a mobile station, going to their places of work, and going directly to their worksite are ways to make vaccination easier. Put a mobile station in front of a concert, where you can get in if you get the vaccine. "I really want to see that musician. I'll get the vaccine."

Improving access to make it more convenient than inconvenient is important, especially when it comes to schools. The American Academy of Pediatrics has a wonderful document for parents to read and sign.[19] It asks them to acknowledge statements such as: "If my child does not receive the vaccine(s) according to the medically accepted schedule, the consequences may include: contracting the illness the vaccine is designed to prevent (the outcomes of these illnesses may include one or more of the following: certain types of cancer, pneumonia, illness requiring hospitalization, death, brain damage, paralysis, meningitis, seizures, and deafness; other severe and permanent effects from these vaccine-preventable diseases are possible as well)." That often changes a parent's mind when they have to sign an acknowledgement of the risk.

Question:

Is there any evidence about vaccination-related adverse pregnancy outcomes?

Dr Benson:

The CDC and FDA are following pregnant women who have been vaccinated through the Vaccine Adverse Event Reporting System (VAERS). Based on data they have collected from more than 120,000 pregnant women who reported receiving vaccines during pregnancy, there have been no adverse outcomes among the pregnant women or their infants from data collected

as of May 24, 2021. There have been pregnant women who received COVID vaccines who miscarried, but the miscarriage rates among those women are the same as in the general population prior to the pandemic, or in the general population who have not received vaccinations.

Animal toxicity studies are conducted in vaccine development. Numerous animal toxicity studies to date have not shown an adverse effect of current vaccines on embryonic fetal or postnatal development of fetuses born to those animals after receipt of vaccine in early or late gestation. We are pretty comfortable at this point that the vaccines are not associated with adverse pregnancy outcomes.

However, pregnant women who have COVID-19 are at increased risk of more severe illness, increased risk of ICU admission, increased risk of the need for mechanical ventilation, and have a higher mortality rate than nonpregnant women. Infection earlier in pregnancy is also associated with an increased risk of adverse fetal outcomes. And in a meta-analysis that included more than 42 studies involving almost 500,000 pregnant women with COVID, the adverse fetal outcomes that were recognized at higher rates than in the prepandemic era were preeclampsia, preterm birth, and stillbirth.

Question:

Can you comment on the more serious complications of vaccines in young people, including myocarditis?

Dr Benson:

It does appear that the mRNA vaccines are associated with an increased risk of myocarditis. According to the *Morbidity and Mortality Weekly Report* published by the CDC, the prevalence is about 1 case per 7 million doses, usually occurring after the second dose, is more common in males, and is more common in people under the age of 30 years. The majority of the cases have been self-limited, only a minority of them have required hospitalization, and symptoms have resolved within 5 to 7 days of onset. The symptoms associated with myocarditis have been relatively mild and included chest pain, low-grade fever, and sometimes shortness of breath and pleuritic chest pain. Most have been associated with modest electrocardiogram findings of ST elevations.

In addition to myocarditis, there have been cases of thrombocytopenic purpura that appears to mimic heparin-induced thrombocytopenia in people who have gotten an adenovirus-based vaccine. This adverse reaction appears to have a predilection for women and has been associated with a small number of fatal cases of cavernous sinus thrombosis or other serious thrombosis disorders among younger women who received an adenovirus vector vaccine. It depends on the study one looks at, but this reaction, although rare overall, appears to occur more commonly in women under the age of 30 years. In the United States, the cases are mostly associated with the Johnson & Johnson vaccine. Overall, the rate is approximately 1 in 7 million doses, so it is still a rare complication of vaccination.

Dr Brown:

These numbers, 1 in 7 million, are meaningful to the medical community but may not be as meaningful to the general population. "It's only 1 in 7 million" may not be terribly effective for someone who just came from the local gas station and put $20 down on a 1 in 10 million shot of winning the lottery, given that the average American spends $200 on the lottery each year.

Responding with a narrative related to the person in front of you may be more helpful. To a 20-year-old who is asking you the question, you might respond, "We had a 20-year-old just last week who passed away from COVID after 3 weeks intubated and on a ventilator in the ICU. His girlfriend and parents were devastated, and his family could not be with him during his last frightening days." Use whatever relatable story that you can share.

Question:

What's your best response to someone who says that vaccine development was rushed, that the vaccines are still experimental, and that they haven't been approved or were only recently approved by the FDA after a long deliberation, so why should I take them or trust them?

Dr Benson:

It is important to note vaccine development for COVID-19 did not involve shortcuts that skipped appropriate steps in the developmental process. All of the same developmental steps were taken, but many were accomplished concurrently rather than consecutively to try and speed the results. By that I mean not only the developmental procedures, but also the manufacturing procedures that needed to be in place to make them available. A massive amount of resources was directed to preclinical development and clinical development in vaccine trials, including investment in sufficient resources to enroll thousands of patients in a few months of time in very large randomized clinical trials.

The logistical setup and implementation of the trials was accelerated, not the developmental process itself. The scientific community completed every single stage of development that we normally would do for a new vaccine including studying them in the laboratory, in animal models, in phase I studies, phase II safety and dose ranging studies, and then in very large phase III randomized trials, each of which was staged to begin when preliminary results from earlier stages indicated it was safe to do so. Rather than, like most vaccines, waiting until they are approved to put together all of the steps for manufacturing, those parts of the process were done in tandem while the clinical trials were being completed. It was understood that money may be spent on a manufacturing process that would never be used, but if we were lucky and any of the candidates were effective, that we would be ready to go when we had the data from the trials.

As Dr Brown said earlier, these vaccine constructs have been in devel-

opment for more than 20 years. The mRNA construct has been used in Ebola virus vaccine development, as well as early development of vaccines for the first SARS and MERS outbreaks a decade ago. The scientific community was not able to fully test them because those outbreaks stopped before the clinical trials could be completed.

Dr Brown:

I also want to note the important role of employers, especially for younger age groups. Employers are instituting creative strategies for encouraging vaccinations. One organization offered an extra Fourth of July holiday day off if at least 70% of employees were vaccinated. Another offered an additional $20 or $30 into their cafeteria fund. These types of creative strategies have subsequently been followed by local, state, or federal government-instituted vaccine mandates for certain groups, which have been extraordinarily effective in getting more people vaccinated.

Summary

In the maelstrom surrounding the COVID-19 pandemic and the vaccine hesitancy debate, an important point has largely been drowned out: The COVID-19 vaccine is one of the greatest triumphs in the history of medicine. In little over a year, the international medical and scientific establishment produced and rolled out a "magic shot" that has already saved millions of lives. With every passing month, there is more and more evidence of just how effective the COVID-19 vaccines truly are.

When confronted with the arguments, objections, and confusion of vaccine-hesitant patients, it is understandable that some scientists and physicians might feel frustrated when speaking with these individuals. Scientists and physicians rely on cold hard facts, on the evidence in front of them, and on the best research available to make important decisions. This approach is amazingly effective at treating sick patients and developing vaccines. But the majority of individuals do not make decisions in the same way. Instead, they use a combination of rational thinking, personal history, and emotion, among other varied factors. Even the most hardened, by-the-book scientist or physician cannot claim to have made every life decision based solely on facts and evidence.

That is why the techniques discussed in this summary have been shown to be so effective: They are all ways to engage patients emotionally. Sitting down calmly with vaccine-hesitant patients, asking them sincere questions, listening compassionately to their concerns, and telling true and impactful stories: These approaches might seem to be less "scientific," but they are certainly more human.

This article was based on a webinar presented by Dr Brown and moderated by Dr Benson on August 3, 2021, titled COVID-19 Vaccine Hesitancy, Crucial Conversations, and Effective Messaging for Patients and Health Care Teams. *The webinar can be viewed here: https://www.youtube.com/watch?v=Vm0g3L2Hu5g.*

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