CMEO
BriefCase

Taking the Long View: Medical Comorbidities that May Shift Treatment Decision-Making

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CME OUTFITTERS

Princy N. Kumar, MD, FIDSA, MACP
Professor of Medicine and Microbiology
Chief, Division of Infectious Diseases and Tropical Medicine
Georgetown University School of Medicine
Washington, DC

Learning Objective

Optimize efficacy and safety profiles of current agents when initiating or switching treatment in patients with HBV.

Patient Case: Khadi

- 58-year-old woman who recently immigrated from Ghana presents to her primary care provider (PCP) for a new patient visit/examination
- She reports mild vasomotor symptoms related to menopause, but nothing that is distressing to her
- Khadi states that she is a little more fatigued recently and not as physically strong as she used to be, but attributes that to getting older
- When asked about anything unusual to note, she mentions that despite drinking a lot of water daily, her urine “seems darker than it should be”
- You order blood work as part of an overall new patient work-up

Virtual Visit

Meet Khadi

CME OUTFITTERS

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- When asked about anything unusual to note, she mentions that despite drinking a lot of water daily, her urine “seems darker than it should be”
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What about Khadi's presentation would change the new patient blood work beyond the routine request (CBC, basic metabolic panel, lipid panel)?

A. Age
B. Vasomotor symptoms
C. Complaints of fatigue, muscle weakness
D. She is an immigrant from Kenya
E. I'm not sure

USPSTF Recommendations for HBV Screening in Adolescents and Adults

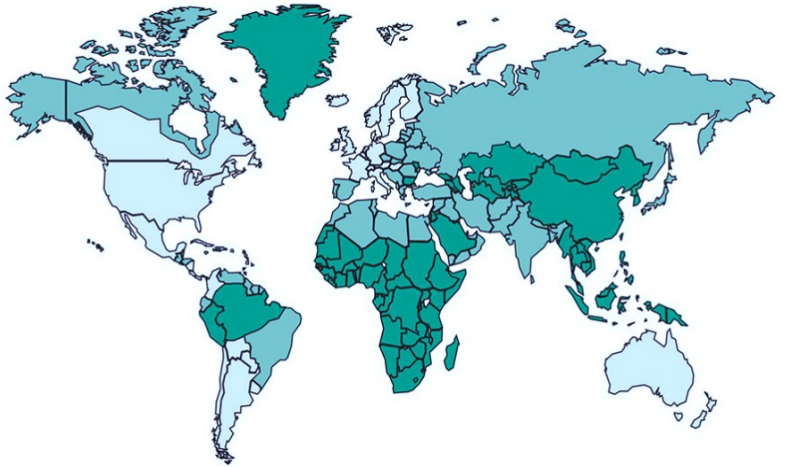
- USPSTF recommends screening for HBV infection in adolescents and adults at increased risk of infection
  - Persons born in countries/regions with moderate prevalence of infection (≥ 2%), such as Asia, Africa, Pacific Islands, and parts of South America
  - U.S.- born persons not vaccinated as infants, whose parents were born in regions with high prevalence (≥ 8%)
  - HIV-positive persons
  - Persons who inject drugs
  - Men who have sex with men
  - Household contacts or sexual partners of persons with HBV infection

U.S. Preventive Services Task Force [USPSTF] Website. 2020. https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/hepatitis-b-virus-infection-screening. Accessed May 28, 2021.

Geographic Distribution of Chronic HBV Infection

Worldwide, 2006[1]

Region	HBV Prevalence ≥ 2%[2]
Africa	All countries
Asia	All countries
Caribbean	Antigua, Barbuda, Dominica, Grenada, Haiti, Jamaica, St. Kitts, St. Lucia, Turks & Caicos Islands
Central America	Guatemala, Honduras
Eastern Europe	All countries except Hungary
Middle East	All countries except Cyprus, Israel
North America	Indigenous populations in northern Canada
South America	Bolivia, Brazil, Colombia, Ecuador, Guyana, Suriname, Venezuela
South Pacific	All countries except non-indigenous populations of Australia and New Zealand
Western Europe	Malta, indigenous populations of Greenland



HBV = Hepatitis B virus

1. Travellers' Health; Yellow Book. http://wwwn.cdc.gov/travel/yellowbookch4-HepB.aspx. Accessed May 28, 2021.
2. Abara WE, et al. *Ann Intern Med*. 2017;167:794-804.

In addition to routine blood work (CBC, basic metabolic panel, lipid panel) what laboratory tests would you order for Khadi?

A. Thyroid panel, complete metabolic panel (adding AST/ALT, bilirubin, albumin) instead of basic metabolic panel
B. Complete metabolic panel (adding AST/ALT, bilirubin, albumin), HBsAg
C. Complete metabolic panel (adding AST/ALT, bilirubin, albumin), HBsAg, anti-HBs, anti-HBc
D. Complete metabolic panel (adding AST/ALT, bilirubin, albumin), HBeAg, anti-HBs, anti-HBc
E. I'm not sure

Hepatitis B Screening and Testing Recommendations

Risk Group	CDC[1]	USPSTF[2]
Persons born in countries with ≥ 2% HBV prevalence	HBsAg Regardless of vaccination status in country or origin	HBsAg anti-HBs anti-HBc
Persons born in United States not vaccinated as an infant and whose parents were born in regions with high HBV endemicity (HBsAg prevalence ≥ 8%)	Test for HBsAg regardless of maternal HBsAg status of not vaccinated as infants in the United States	HBsAg anti-HBs anti-HBc
Men who have sex with men	HBsAg anti-HBs anti-HBc	HBsAg anti-HBs anti-HBc
Persons who inject drugs	HBsAg anti-HBs anti-HBc	HBsAg anti-HBs anti-HBc
Persons with HIV infection	HBsAg anti-HBs anti-HBc	HBsAg anti-HBs anti-HBc
Household, needle-sharing, or sexual contact with persons with HBV infection	HBsAg anti-HBs anti-HBc	HBsAg anti-HBs anti-HBc

HBc = hepatitis B core antigen; HBsAg = hepatitis B surface antigen;

1. Weinbaum CM, et al. *MMWR* Recomm Rep. 2008;57(RR-8):1-20. 2. U.S. Preventive Services Task Force [USPSTF] Website. 2020. https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/hepatitis-b-virus-infection-screening. Accessed May 28, 2021.

Patient Case: Khadi

- Khadi's serologic results return:
  - HBsAg: positive
  - Total anti-HBc: positive
  - IgM anti-HBc: negative
  - anti-HBs: negative
  - HBV DNA: 3,000 IU/ml
  - ALT: 70 u/L
  - AST: 60 u/L
  - Total bilirubin: 2.2 mg/dL
  - Albumin: 3.4 mg/dL

ALT = alanine transaminase; AST = aspartate aminotransferase; dL = deciliter; DNA = deoxyribonucleic acid; IgM = immunoglobulin; IU = international unit; L = liter; ml = milliliter; mg = milligram; u = units

Interpretation of HBV Serologic Test Results

Serologic Test Result	HBsAg	Total Anti-HBc	IgM Anti-HBc	Anti-HBs
Detected following vaccination or for 3-6 months following receipt of HBIg	−	−	−	+
• False positive (susceptible) • Past infection (resolved) • "Low level" chronic infection (unlikely to be infectious)	−	+	−	−
Chronic Hepatitis B (CHB) infection	+	+	−	−
Past infection, with recovery, immunity to new infection	−	+	−	+
Acute infection	−	+	+	−
Early acute infection	+	−	−	−
Never infected, susceptible	−	−	−	−

- **HBsAg:** Detected in high levels in serum during acute or chronic HBV infection. Its presence indicates the person is infectious.
- **anti-HBc:** Appears at the onset of symptoms in acute HBV and persists for life. Indicates previous or ongoing infection.
- **IgM antibody to hepatitis B core antigen (IgM anti-HBc):** Positivity indicates recent infection with HBV (≤ 6 months). Its presence indicates acute infection.
- **anti-HBs:** The presence of anti-HBs is generally interpreted as indicating recovery or immunity from HBV infection. Also present in a person who has been vaccinated.

HBIg = hepatitis B immune globulin

Centers for Disease Control and Prevention [CDC] Website. https://www.cdc.gov/hepatitis/resources/professionals/training/serology/training.htm. Accessed May 28, 2021.

Imaging Evaluation in Patients with CHB

- Liver ultrasound with or without serum alpha-fetoprotein (AFP) every 6 months
  - More frequent monitoring or other imaging modalities such as CT or MRI with and without contrast may be indicated to evaluate new liver lesions

Non-invasive Methods for Assessing Cirrhosis and Fibrosis

Elastography

- Transient elastography (TE)
- Magnetic resonance elastography (MRE)
- 2D shear wave elastography (SD-SWE)

Serum Biomarkers

- FIB-4
- FibroTest
- FibroSure
- Aspartate aminotransferase-platelet ratio index (APRI)

CT = computed tomography; MRI = magnetic resonance imaging

Terrault NA, et al. *Hepatology*. 2018;67(4):1560-1599.

What is your next step?

A. Initiate treatment
B. Monitor Khadi and check again in 6 months
C. Refer to specialist
D. I’m not sure

Treatment and Management of Patients with HBV*

Cirrhosis	HBV DNA (IU/mL)	ALT (U/L)	Management
YES	Any	Any	• **TREAT** with antiviral medication • Monitor HBV DNA and ALT every 6 months • Refer to specialist for screening endoscopy and, if needed, for other cirrhosis-related complications • HCC surveillance, including in persons who become HBsAg- • All patients with decompensated cirrhosis† should be referred to a hepatologist
NO	> 2,000	Elevated‡	• **TREAT** with antiviral medication • Monitor HBV DNA and ALT every 6 months • Monitor HBeAg and anti-HBe every 6 months in patients who are HBeAg+ at the time of treatment initiation to evaluate for seroconversion from HBeAg+/anti-HBe- to HBeAg-/anti-HBe+ • Check HBsAg annually if/when HBeAg-
		Normal	• **Monitor** HBV DNA and ALT every 6 months • Liver fibrosis assessment every 2-3 years
	≤ 2,000	Elevated‡	• **Evaluate** other etiologies for elevated ALT • Monitor HBV DNA and ALT every 6 months
		Normal	• **Monitor** HBV DNA and ALT every 6 months and HBsAg every year for seroclearance

HBeAg = hepatitis B e-antigen

*In contrast to other HBV guidelines that have incorporated HBeAg status into treatment initiation decisions for non-cirrhotic HBsAg+ patients, this guidance for PCPs uses only HBV DNA and ALT to determine initial treatment indication in non-cirrhotic HBsAg+ patients. †Patients should be considered to have decompensated cirrhosis and promptly referred to a hepatologist if any of the following are present: jaundice, ascites, variceal hemorrhage, hepatic encephalopathy, or a Child-Turcotte-Pugh (CTP) score ≥ 7 (see Hepatitis B Online CTP calculator). ‡Elevated ALT defined as > 25 U/L in females and > 35 U/L in males that is persistent for at least 3-6 months

Tang AS, et al. Hepatitis B Online Website. 2020. https://www.hepatitisB.uw.edu/hbv-pcw/guidance. Accessed May 29, 2021.

Patient Case: Khadi

- Treatment is initiated with tenofovir disoproxil fumarate (TDF) 300 mg daily
- Khadi is scheduled for routine follow-up for 3-4 months in the first and every 6 months thereafter
  - ALT
  - HBV DNA
  - Imaging evaluation for cirrhosis and hepatocellular carcinoma (HCC) annually

EASL. *J Hepatol*. 2017;67(2):370-398.

Counseling Patients About Risk of Disease Transmission

- Horizontal transmission is the most important route of transmission in low endemic countries like the U.S.
- Approximately 3%-20% of persons living in households with persons with CHB have serologic evidence of chronic infection
- Risk highest among sexual partners and children
- Sharing of food and utensils, hugging and kissing do not convey transmission risk
- High risk associated with sharing toothbrushes, razors, and contact with blood or body fluids

Kushner T, et al. *Clin Liver Dis* (Hoboken). 2019;13(4):93-97.

Who Should Be Vaccinated? Adults Who Are Recommended to Receive the Hepatitis B Vaccine

• At risk through sexual exposure	Sex partners of HBsAg+ persons
	Sexually active persons not in long-term, mutually monogamous relationship
	Persons seeking evaluation or treatment for sexually transmitted infection
	Men who have sex with men
• History of current or recent injection drug use	
• At risk for infection by percutaneous or mucosal exposure to blood	Household contacts
	Residents and staff of facilities for developmentally disabled persons
	Health care public safety personnel at risk for exposure to blood or blood contaminated body fluids
	Hemodialysis patients and predialysis, peritoneal dialysis, and home dialysis patients
	Person with diabetes mellitus who are age < 60 and ≥ 60 at the discretion of the treating clinician
• International traveler to countries with high or intermediate levels of endemic HBV	
• Persons with hepatitis C infection, chronic liver disease (including, but not limited to cirrhosis, fatty liver disease, alcoholic liver disease, autoimmune hepatitis, ALT or AST level greater than 2x upper limit of normal	
• Persons with human immunodeficiency virus (HIV)	
• Incarcerated persons	
• Other persons seeking protection from HBV infection (even without acknowledgement of a specific risk)	

Schillie S, et al. *MMWR Morb Mortal Wkly Rep*. 2018;67(15):455-458.

Patient Education and Counseling: Encouraging a Healthy Lifestyle

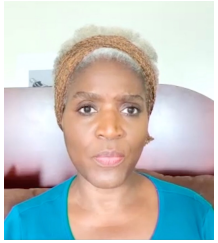
- Schedule regular visits with your liver specialist or health care provider
- Get the hepatitis A vaccine
- Avoid drinking alcohol and smoking
- Talk to your provider before starting any herbal remedies or vitamin supplements
- Everything you eat, drink, breathe, or absorb through the skin is eventually filtered by the liver!
- Eat a healthy diet
- Avoid eating raw or undercooked shellfish
- Check for signs of mold on food
- Reduce your stress through healthy diet, rest, and exercise
- Check with your pharmacist about any over-the-counter drugs
  - Acetaminophen
  - NSAIDs

PROTECT YOUR LIVER!

HEPATITIS B FOUNDATION

Hepatitis B Foundation Website. https://www.hepb.org/assets/Uploads/Living-with-Chronic-Hepatitis-B.pdf. Accessed May 29, 2021.

Patient Case: 18-Month Visit



- Khadi has been diligent about her follow-up visits and is doing well

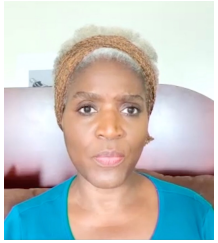
Scene 2: Virtual Visit

18-month monitoring visit

What is your next step?

A. Discontinue TDF
B. Supplement her TDF with vitamin D3
C. Prescribe risedronate monthly
D. Monitor with a DEXA scan yearly
E. I’m not sure

Patient Case: 18-Month Visit



- Khadi has been diligent about her follow-up visits and is doing well
- In reviewing her history over the past 6 months, she shares that 4-months ago, she fell and fractured her wrist
- The healing process was unremarkable
- Given she is now 59-years-old, you order a DEXA scan
- DEXA scan T-score is -1.8 indicating osteopenia

Bone Loss in CHB Viral Infection

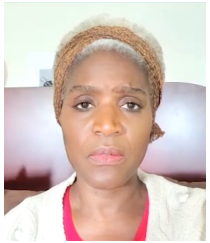
- A result of cumulative and time-dependent interactions between the patient's risk factors for osteoporosis such as viral load, associated inflammation, and use of antiviral drugs[1]
- But, independent of antiviral treatment, the presence of CHB infection increases the risk of bone alterations[1]
- Bone density study is recommended at baseline and during treatment for persons with history of fracture or osteopenia[2]

1. Dessordi R, et al. *Sci Rep*. 2021;11(1):10162. 2. Terrault NA, et al. *Hepatology*. 2018;67(4):1560-1599.

Virtual Visit

3 years later

Patient Case: 3 Year Follow-up



- Khadi, now 61-years-old, continues to be diligent about her follow-up visits and is doing well
- DEXA scan T-score is -2.9 indicating she has progressed to osteoporosis

What is your next step?

A. Prescribe risedronate monthly
B. Continue to monitor
C. Switch from TDF to TAF
D. I’m not sure

Risk Factors for Progression to Osteoporosis

- The prevalence of osteoporosis in CHB varies widely, ranging from 20-50%
- Modifiable risk factors, independent of CHB, impact the risk of osteoporosis
  - Inadequate nutritional absorption
  - Lack of physical activity
  - Obesity
  - Smoking
  - Alcohol consumption
  - Stress

Pouresmaeili F, et al. *Ther Clin Risk Manag*. 2018;14:2029-2049.

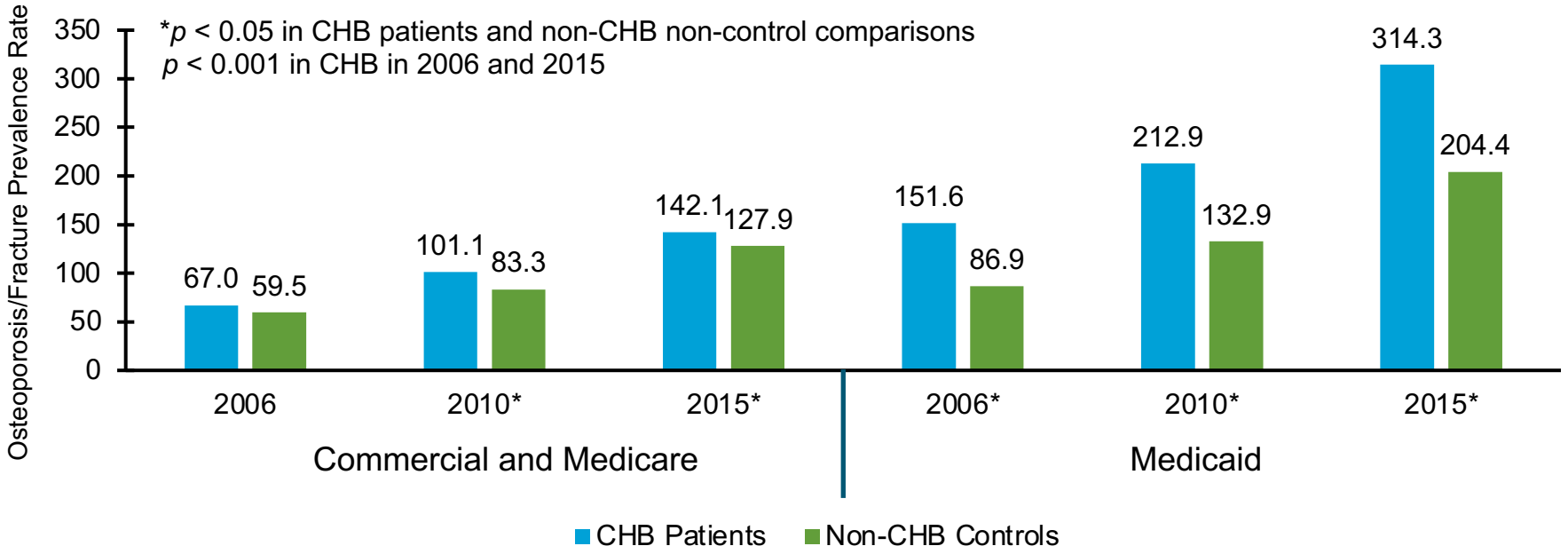
TDF and Bone Health

- Although highly effective with a negligible risk of resistance, the relatively high dose leads to high concentrations of circulating tenofovir which can result in kidney and bone toxicity with long-term use[1]
- AASLD guidelines recommend that in the case of tenofovir-associated renal dysfunction and or osteoporosis/osteomalacia, TDF should be discontinued and substituted with an alternate NA with consideration for previous drug resistance[2]

AASLD = The American Association for the Study of Liver Diseases; NA = nucleotide analog

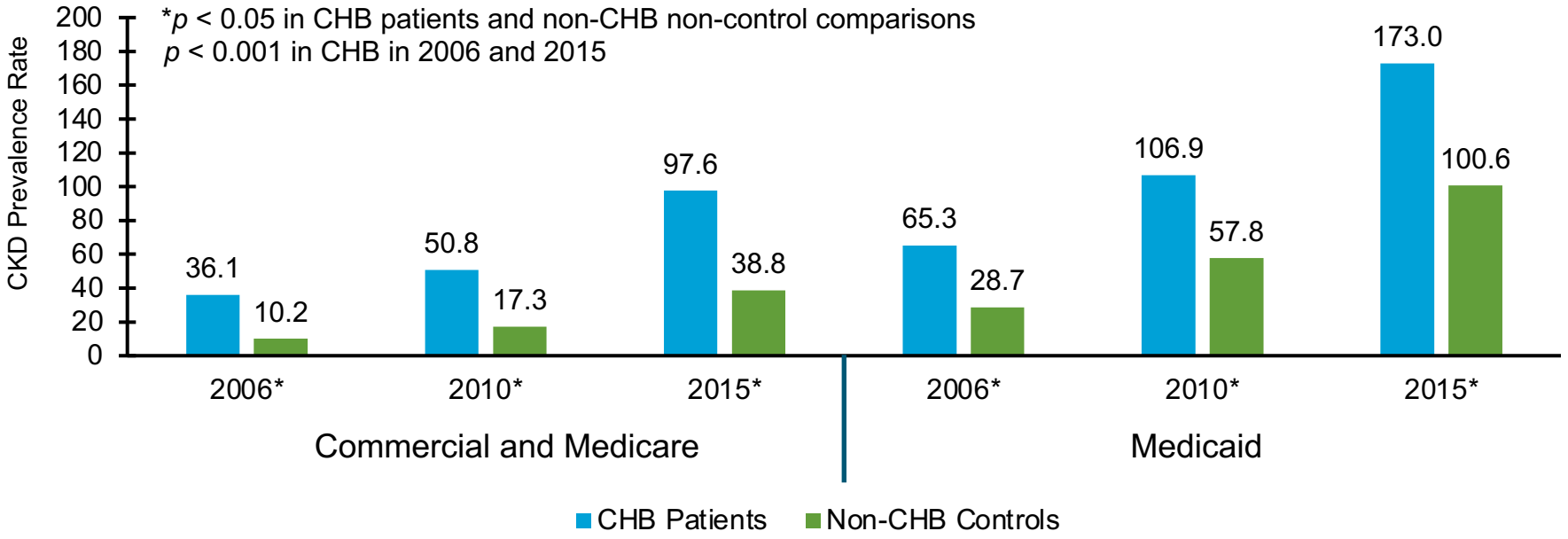
1. Lampertico P, et al. *Lancet Gastroenterol Hepatol*. 2020;5(5):441-453. 2. Terrault NA, et al. *Hepatology*. 2018;67(4):1560-1599.

Osteoporosis and/or Fracture Prevalence per 1,000 Persons



Commercial and Medicare: 2006 CHB patients n = 3,819; 2010 CHB patients n = 9,958; 2015 CHB patients n = 9,094; 2006 non-CHB patients n = 9,546; 2010 non-CHB patients n = 26,814; 2015 non-CHB patients n = 26,337
Medicaid: 2006 CHB patients n = 1,425; 2010 CHB patients n = 2,067; 2015 CHB patients n = 2,278; 2006 non-CHB patients n = 3,141; 2010 non-CHB patients n = 4,582; 2015 non-CHB patients n = 5,773
Nguyen MH, et al. *Hepatology*. 2019;69(3):959-973.

Chronic Kidney Disease (CKD) Prevalence per 1,000 Persons



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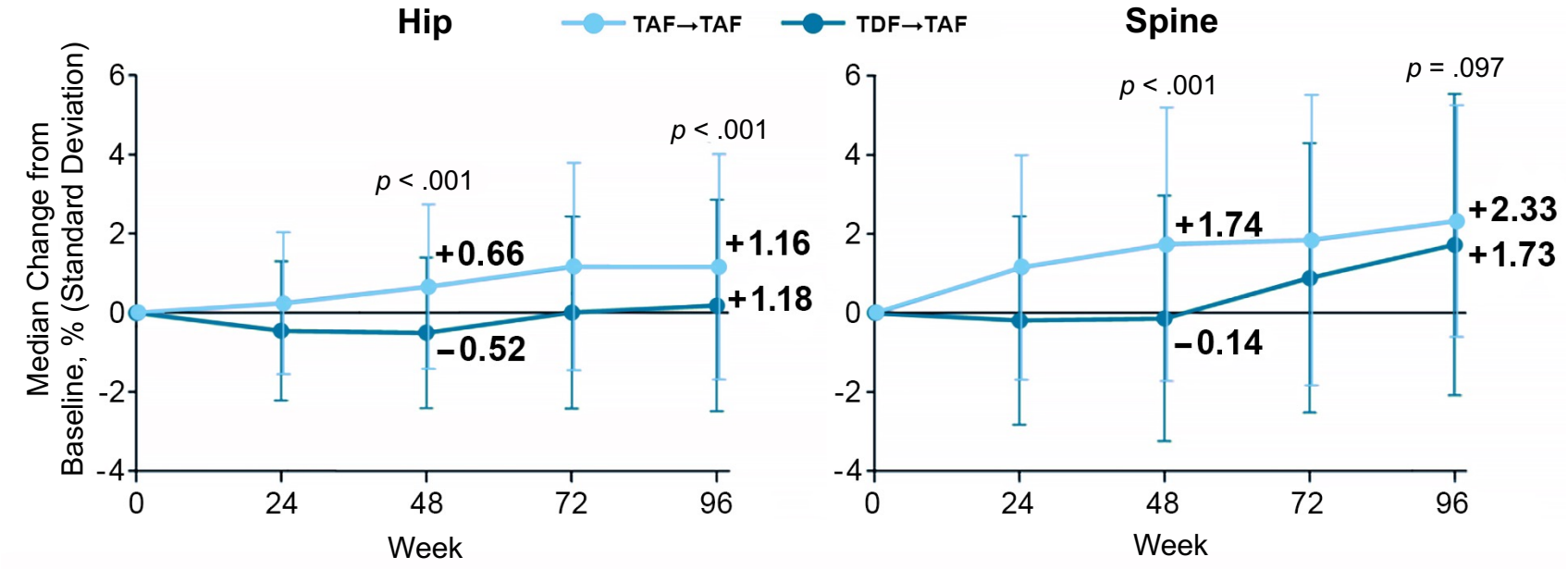
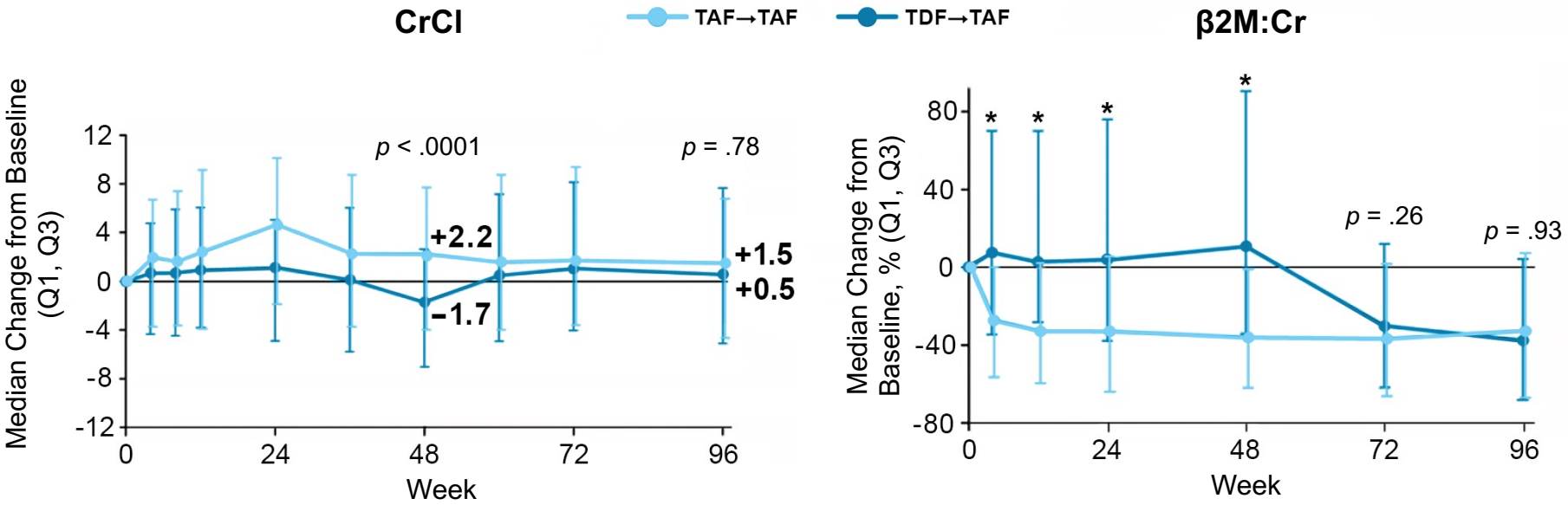
Bone Health: Impact of Switching from TDF to TAF at 96 Weeks

Hip and Spine Bone Mineral Density Through Week 96



Khalili M, et al. Presented at ACG 2020 Virtual Annual Scientific Meeting & Postgraduate Course. October 23-28, 2020.

Changes in Renal Parameters at 96 Weeks After Switching from TDF to TAF



β2M:Cr = β2-microglobulin creatinine; CrCl = creatinine clearance

Khalili M, et al. Presented at ACG 2020 Virtual Annual Scientific Meeting & Postgraduate Course. October 23-28, 2020.

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- Raise clinical suspicion of HBV infection in immigrants from countries of moderate or high HBV prevalence and initiate screening
- Recognize that patients with CHB are at risk for bone loss independent of their antiviral treatment
- Align treatment initiation and switching decisions to AASLD guideline recommendations in the presence of renal impairment and/or bone loss

Visit the

Liver Disease Hub

This activity and others in the series available on the Liver Disease Hub where you will find free resources and education for health care providers

https://www.cmeoutfitters.com/liver-hub/

Hepatitis B Patient Education Hub

A robust hub of patient education and resources for your patients to learn more about hepatitis B

https://www.cmeoutfitters.com/hbv-patient-education-hub/

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