

ORIGINAL RESEARCH

European AIDS Clinical Society (EACS) guidelines for the clinical management and treatment of chronic hepatitis B and C coinfection in HIV-infected adults

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Objectives

With the decline in HIV-associated morbidity and mortality following the introduction of highly active antiretroviral therapy (HAART), liver disease has emerged as a major cause of death in HIV/hepatitis B virus (HBV) and HIV/hepatitis C virus (HCV) coinfecting persons. Therefore, screening for underlying viral hepatitis coinfection and the provision of management and treatment recommendations for patients with chronic viral hepatitis are of great importance in preventing, as far as possible, the development of liver disease. With the introduction of new agents for the treatment of hepatitis B and increased knowledge of how best to manage hepatitis C, an update of current guidelines for management of HBV and HCV coinfection with HIV is warranted.

Summary

Clearly, all HIV-infected patients should be screened for hepatitis A, B and C, taking into account shared pathways of transmission. Patients who are seronegative for hepatitis A and B should be considered for vaccination. In HIV-infected patients with chronic hepatitis B, the first important differentiation is whether HAART is required or not. In the setting of stable HIV infection, with no need for HAART, several treatment options are available, namely treatment with interferon, early initiation of HAART, or selective non-HIV active anti-HBV nucleoside therapy, with the aim of achieving undetectable HBV DNA levels. In most cases, undetectable HBV DNA can only be achieved with combination therapy.

With regard to hepatitis C, individualized tailoring of the duration of HCV therapy is advisable, taking into account rapid or delayed virological response. In patients who do not achieve at least a 2 log drop in HCV RNA at week 12, treatment can be terminated because of the low probability of achieving sustained virological response. Overall, with the currently available treatment algorithms, HCV can be eradicated in over 50% of patients. Therefore, HCV therapy should be considered and discussed with the patient if an indication for HCV therapy (elevated liver enzymes, positive HCV RNA and >F1 fibrosis) is present.

Conclusions

Management of underlying hepatitis B and/or C in patients with HIV infection is of great importance in preventing liver disease-associated morbidity and mortality.

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Introduction

The introduction of highly active antiretroviral therapy (HAART) in 1996 was associated with a dramatic decline in HIV-associated morbidity and mortality. Subsequently,

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however, liver disease caused by chronic hepatitis B virus (HBV) and/or hepatitis C virus (HCV) coinfection in HIV-infected individuals has emerged as a leading cause of hospitalization and death in the coinfecting population. Indeed, a recent analysis from the Data collection on Adverse events of Anti-HIV Drugs (DAD) study demonstrated that liver-related death was the most frequent cause of non-AIDS-related deaths, with a strong association between immune deficiency and risk of liver-related death [1]. Therefore, the best possible management of underlying HBV or HCV coinfection in HIV-infected individuals is a priority for the prevention of disease progression, particularly once HIV infection has been controlled.

Several guidelines with regard to management of coinfection have been introduced. These guidelines, endorsed by the European AIDS Clinical Society, result from the short statement of the first European Consensus Conference on the treatment of chronic hepatitis B and C in HIV-coinfecting patients as well as from the updated recommendations of the HCV/HIV International Panel [2,3]. Nevertheless, with new drugs becoming available for treatment of hepatitis B and results being reported from new HCV trials looking at different dosages and durations of polyethylene glycol (PEG)-interferon/ribavirin (RBV) HCV combination therapy, an update of the currently available hepatitis guidelines seems advisable. Unfortunately, many questions in the field of coinfection cannot be answered fully at this time because of the lack of randomized controlled clinical trials in this particular group of patients. However, in order to achieve the highest quality assurance for the care of coinfecting individuals, regular updates of treatment recommendations

would appear to be useful in order to ensure that the highest standards of clinical care are delivered.

Summary of guidelines

General recommendations

All HIV-infected patients should be screened for hepatitis A virus (HAV), HBV and HCV, taking into account the common routes of transmission for these viruses. Patients who have negative HAV and HBV serology and are HIV positive should receive vaccination according to the schedule provided in Table 1. In patients who are diagnosed with either chronic hepatitis B or C, psychological, social and medical support should be made available to stop patients with a high alcohol intake from drinking or to at least strongly advise them to limit alcohol consumption. Increased alcohol consumption has been identified as an important co-factor in liver disease progression. With regard to further harm reduction, it would be advisable to point out that opioid substitution therapy in patients with active drug abuse can be considered a first step towards cessation of active drug use. Taking into account the recent outbreak of acute hepatitis C among various men-who-have-sex-with-men (MSM) communities in London, Berlin, Amsterdam, and Paris, adequate counselling is recommended reinforcing the use of condoms and safe sex practices [4].

Management of chronic hepatitis B

Medications licensed in Europe and the USA for the treatment of HBV infection include interferon- α , PEG-

Table 1 General recommendations for counselling in patients with HIV and hepatitis coinfection

Screening

1. All HIV-infected patients should be screened for hepatitis C at diagnosis and then on an annual basis (if still engaged in any risk behaviour). Screening for HCV in HIV-infected patients should be performed using a third-generation anti-HCV antibody test. A positive result should be confirmed by evaluation of the presence of HCV RNA and the genotype should be determined. Patients with risk factors (ongoing injecting drug use; mucosal traumatic sex; cocaine use) with an unexplained increase in hepatic transaminases and a negative HCV antibody test should be tested for HCV RNA for early detection of acute infection.
2. HIV-infected patients should be screened for anti-HAV IgG, HBsAg, anti-HBc IgG and anti-HBs antibodies.
3. Hepatitis delta antibodies should be screened for in all HBsAg-positive patients.

Vaccination

4. Patients lacking anti-HAV IgG antibodies and/or HBsAg and anti-HBV antibodies should be offered vaccination for the respective virus to prevent infection, regardless of their CD4 cell count. The response to the vaccine is influenced by the CD4 cell count and level of HIV RNA. In patients with low CD4 cell counts (<200 cells/ μ L) and ongoing HIV replication, HAART should be initiated first prior to vaccination. In the case of an insufficient response (anti-HBs <10 IU/L) re-vaccination should be considered. Double dose re-vaccination (40 μ g) at 3–4 vaccination time-points (months 0, 1, 6 and 12) may help to improve response rates to vaccination [5].
5. Patients who failed to seroconvert after HBV vaccination and remain at risk for HBV infection should be monitored annually for serological markers of HBV infection.

Prevention/support

6. Psychological, social and medical support should be made available to stop patients with a high alcohol intake from drinking or to strongly advise them to limit alcohol consumption.
7. Opioid replacement therapy in patients with active drug abuse as a step towards cessation of active drug use should be considered up front; help provided (e.g. through needle- and syringe-exchange programmes) reduces the risk of HCV reinfection (harm reduction strategy).
8. As HBV and HIV and occasionally HCV are transmitted sexually, adequate counselling, including the use of condoms, is advisable. Mucosal traumatic sexual practices associated with a high risk of blood contact should be discouraged.

HAART, highly active antiretroviral therapy; HAV, hepatitis A virus; HBc, hepatitis B virus core; HBsAg, hepatitis B virus surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; IgG, immunoglobulin G.

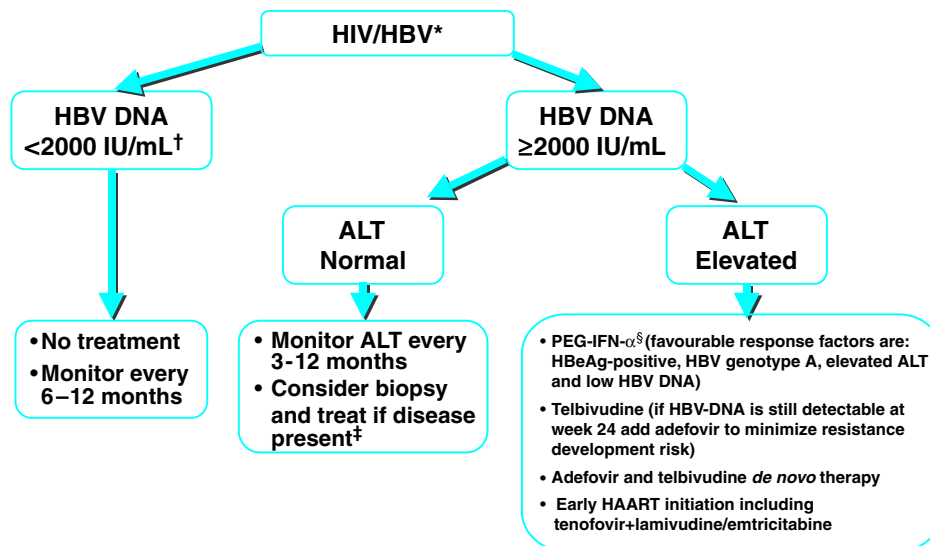


Fig. 1 Management and therapeutic options in compensated hepatitis B virus (HBV)/HIV-coinfected patients with no immediate indication for anti-HIV therapy (CD4 count > 350 cells/ μ L). Patients with replicating HBV and normal liver enzymes may have significant liver damage, so assessment of liver damage should be considered; liver damage may be assessed using either a liver biopsy or noninvasive tools, including serum fibrosis markers or FibroScan. While a liver biopsy may provide additional information on inflammation and other lesions (e.g. steatosis), noninvasive markers can be used at more frequent intervals. *Chronic HBV infection, defined as hepatitis B virus surface antigen (HBsAg)-positive for > 6 months. †Serum HBV DNA levels have been demonstrated to be associated with a linear increased risk for development of liver cirrhosis and hepatocellular carcinoma (HCC); please note that the calculation from copies to IU/mL varies depending on which respective test assay was used; in general, 1 IU/mL equals around 5 copies or genome equivalents; one picogram HBV DNA equals 2.8×10^5 genomes/mL. ‡METAVIR \geq A2 and/or F2. §Treatment length: 48 weeks for polyethylene glycol-interferon- α (PEG-IFN- α); for the nucleoside reverse transcriptase inhibitors (NRTIs): HBsAg seroconversion + 6 months. In those not requiring highly active antiretroviral therapy (HAART) and on treatment with telbivudine \pm adefovir, or those on HAART where the NRTI backbone needs to be changed, anti-HBV therapy may be stopped cautiously in HBV envelope antigen (HBeAg)-positive patients who have achieved HBe seroconversion or HBs seroconversion for at least 6 months or after HBs seroconversion for at least 6 months in those who are HBeAg-negative. ALT, alanine aminotransferase.

interferon, lamivudine (3TC), adefovir, entecavir and telbivudine (so far only licensed in the USA and selected European countries). Tenofovir (TDF) and emtricitabine (FTC) are approved for HIV treatment and are also active against HBV. The optimal goal of treatment of HBV infection is to achieve HBV surface antigen (HBsAg) clearance with anti-HBV surface antibody (HBsAb) seroconversion. This, however, is only achieved in a very small number of patients. The more realistic goal is long-term suppression of HBV replication to reduce liver inflammation and stop or delay progression of hepatic fibrosis. The greatest challenge currently is avoidance of the development of HBV-associated drug resistance, which under HBV monotherapies with drugs such as 3TC has been described to occur in more than 80% of patients after 5 years of treatment. Other drugs are more stable with regard to the development of resistance; however, if full suppression of HBV RNA in an ultrasensitive assay is not achieved, an add-on of an HBV drug with a different resistance profile should be considered. The currently developed treatment algorithms for HIV/HBV coinfection take into account HBV DNA levels, severity of liver disease,

alanine aminotransferase (ALT) levels, CD4 cell count and indications for use of HAART. In patients with chronic hepatitis B and HIV infection, the first question to ask is whether patients have an indication for HAART. Figure 1 summarizes the possible management algorithm and therapeutic recommendations in HIV/HBV-coinfected patients without an indication for anti-HIV therapy (which generally would be a CD4 count > 350 cells/ μ L [no initiation of HIV treatment], although in HBV-coinfected patients a CD4 count < 500 cells/ μ L could be considered as the cut-off for starting anti-HIV treatment). Given the lack of consistent data on the long-term efficacy of antiviral treatment with adefovir and/or telbivudine as monotherapy or combination treatment in HIV-seropositive individuals, these options may at this time be better reserved for patients with advanced fibrosis (i.e. F3–F4 using the METAVIR score). Monotherapy with entecavir, which was not long ago considered an option, is now considered contraindicated as anti-HIV activity of entecavir was recently described, which led to the emergence of resistance mutations relevant for HIV therapy (M184V) [6].

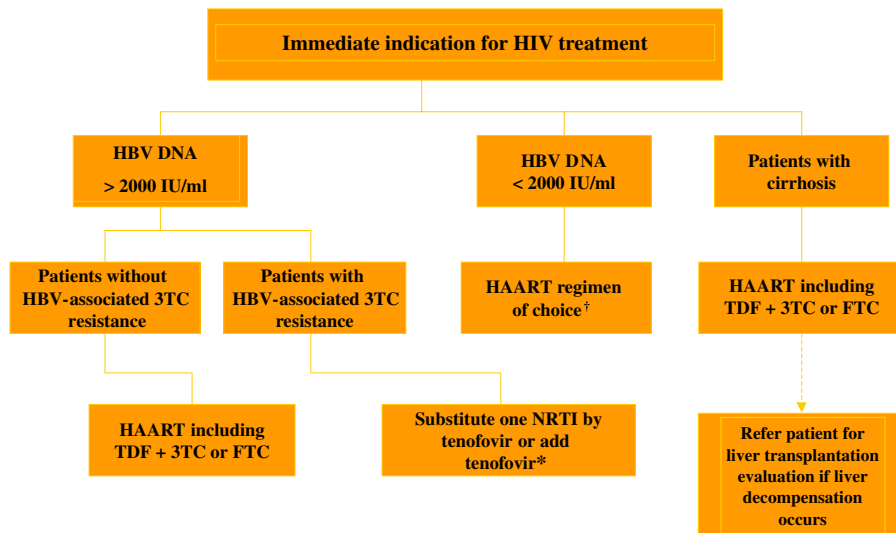


Fig. 2 Management and therapeutic options in compensated or cirrhotic hepatitis B virus (HBV)/HIV-coinfected patients with an indication for HIV treatment [CD4 count <350 cells/ μ L or already on highly active antiretroviral therapy (HAART)]. *If feasible and appropriate from the perspective of maintaining HIV suppression. In some cases of tenofovir (TDF) intolerance (i.e. renal disease), entecavir 1 mg/day may be advisable. †Some experts strongly believe that any HBV-infected patient requiring HAART should receive TDF + lamivudine (3TC) or emtricitabine (FTC) unless they have a history of TDF intolerance. NRTI, nucleoside reverse transcriptase inhibitor.

In Fig. 2, management and therapeutic options are provided for compensated or cirrhotic HBV/HIV-coinfected patients who have an indication for HIV treatment or are already on HAART. In patients with an indication for HAART, a regimen containing TDF plus 3TC or FTC is favoured in order to delay development of 3TC or FTC resistance against HBV (the HBV resistance rate with 3TC after 2 years is almost 50% in HIV/HBV-coinfected patients). In patients who have already developed 3TC/FTC-resistant HBV, TDF should be added or should replace 3TC for HBV treatment (the latter only if appropriate with respect to the treatment of HIV). Data for HBV-monoinfected individuals on adefovir \pm 3TC suggest that combination therapy may delay the development of resistance. The question of whether entecavir can or should be used along with TDF in patients who have not fully suppressed HBV DNA with TDF \pm 3TC (FTC) cannot be answered at this time because of the lack of available data. To date, no clear evidence of development of HBV-resistance mutations under TDF in patients with ongoing HBV replication has been presented.

Management of chronic hepatitis C

HCV treatment offers the possibility of eradicating HCV within a defined treatment period. This is potentially advantageous for the subsequent management of the patient with HIV infection. Every patient should therefore be considered for treatment when the benefits of therapy

outweigh the risks. Benefits of therapy also need to be seen in the context of faster liver fibrosis progression in HIV/HCV coinfection and improved HCV treatment outcome under optimized management in these patients. Information on liver fibrosis staging is important for making therapeutic decisions in coinfecting patients. However, a liver biopsy is not mandatory for decisions on treatment of chronic HCV infection. Current therapy is particularly recommended in patients with a high likelihood of achieving a sustained virological response (SVR), i.e. patients infected with genotype 2 or 3 and those infected with genotype 1 if the viral load is low (<400 000–500 000 IU/mL). More recently, insulin resistance [which can be determined using the homeostasis model assessment of insulin resistance (HOMA IR) score] has been repeatedly reported as a negative predictor of achievement of SVR and therefore may also be considered during pretreatment evaluation. Where a liver biopsy or noninvasive tests for gauging hepatic fibrosis (e.g. elastometry by FibroScan, Echosens, France) have demonstrated lower grades of liver fibrosis (F0–F1), regardless of HCV genotype, treatment can be deferred. It is especially important to perform a liver disease stage assessment in patients with a low likelihood of achieving SVR.

The combination of PEG-interferon- α (PEG-IFN- α) and weight-based RBV is the treatment of choice for HCV infection. The standard dose for PEG-IFN- α -2a is 180 μ g/kg body weight once weekly, and for PEG-IFN- α -2b it is 1.5 μ g/kg body weight once weekly. A weight-adapted dose

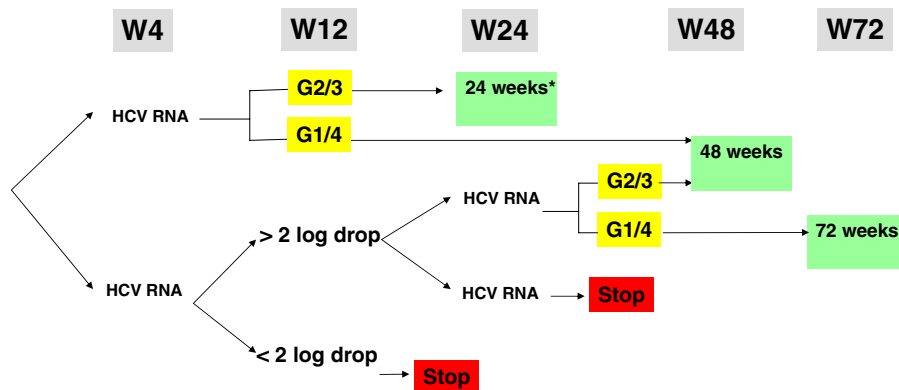


Fig. 3 Proposed optimal duration of hepatitis C virus (HCV) therapy in HCV/HIV-coinfected patients. W, week; G, genotype. *In patients with baseline low viral load (<400 000 IU/L) and minimal liver fibrosis.

Table 2 Diagnostic procedures for hepatitis C in HIV coinfection

Diagnosis of hepatitis C

HCV-Ab (positive 1–5 months after infection; may rarely be lost with immunosuppression)

HCV RNA levels *(while not prognostic for progression, it is for response to treatment)

Status of liver damage

Grading of fibrosis (e.g. FibroScan, liver biopsy and serum fibromarkers[†])

Hepatic synthetic function (e.g. coagulation, protein, albumin and CHE)

Ultrasound and AFP every 6 months in patients with cirrhosis (gastroscopy upon diagnosis of cirrhosis and every 1–2 years thereafter)

Before HCV treatment

HCV genotype and serum HCV RNA

Autoantibodies (ANA, SMA, ANCA and LKM1)

TSH and thyroid autoantibodies if applicable

Monitoring of HCV treatment

Differential blood count and liver enzymes every 2–4 weeks

HCV RNA at week 4 (to evaluate rapid virological response), weeks 12, 24 and 48 (72 if applicable), and 24 weeks after stopping HCV therapy

CD4 cell count every 12 weeks

TSH every 12 weeks

*Low viral load is defined as <400 000 IU/L when using polyethylene glycol-interferon- α plus ribavirin. There is no standard conversion formula for converting the amount of HCV RNA reported in copies/mL to the amount reported in IU. The conversion factor ranges from about 1 to 5 HCV RNA copies per IU.

[†]Serum fibromarkers include aspartate aminotransferase to platelet ratio index (APRI), FIB-4, hyaluronic acid, Fibrotest (Biopredict, Paris, France), Forns and other indexes.

AFP, alpha-fetoprotein; ANA, antinuclear antibodies; ANCA, Neutrophil Cytoplasmic Antibodies; CHE, cholinesterase; HCV-Ab, hepatitis C virus antibody; LKM1, liver-kidney-microsomal autoantibodies; SMA, anti-smooth muscle autoantibodies; TSH, thyroid-stimulating hormone.

of RBV of 1000 (weight <75 kg) to 1200 (weight >75 kg) mg daily [administered twice a day (bid)] is recommended for all genotypes. The primary aim of anti-HCV treatment is sustained virological response, defined as undetectable serum HCV RNA 24 weeks after the end of therapy, evaluated using ultrasensitive PCR tests (<10 IU/mL). If chronic hepatitis C is detected early in the course of HIV infection (before the initiation of HAART), treatment for chronic HCV is advised. However, if a coinfecting patient has severe immunodeficiency (CD4 count <200 cells/ μ L), the CD4 count should be improved using HAART prior to commencing anti-HCV treatment. Patients with a CD4 relative percentage >25% are more likely to achieve SVR than those with lower CD4 percentages [7]. If an early

virological response of at least a 2 log₁₀ reduction in HCV RNA compared with baseline is not achieved at week 12, treatment should be discontinued, as an SVR is unlikely (Fig. 3).

During PEG-IFN- α plus RBV therapy, didanosine is contraindicated [8]. Stavudine and zidovudine should also be avoided if possible. The role of abacavir is uncertain at this point, but cohort data suggest lower SVR occurs in patients receiving abacavir-containing HAART [9]. A possible explanation may be the impairment of RBV phosphorylation by abacavir.

In patients with acute HCV infection, HCV therapy is recommended if HCV RNA is confirmed as positive (in two tests 1 week apart) by week 12 post HCV transmission, as

Table 3 Classification of and interventions for HCV/HIV-coinfected patients who are nonresponders/relapsers to prior interferon-based therapies

Category	Recommended intervention
Suboptimal prior treatment schedules <ul style="list-style-type: none"> • Interferon (monotherapy or with ribavirin) • Low ribavirin doses • Short length of therapy 	Re-treatment using combination therapy with PEG-interferon- α plus weight-based ribavirin doses
Limiting toxicities and poor adherence Virological failure	Optimal support (SSRI, paracetamol/NSAID, pharmacists, use of haematopoietic growth factors [14]) Wait until new antivirals come to the market in the rest

NSAID, non-steroidal anti-inflammatory drugs; PEG, polyethylene glycol; SSRI, selective serotonin reuptake inhibitors.

SVR rates following treatment of acute HCV infection are higher than for treatment of chronic HCV. The procedures for diagnosis of hepatitis C, assessment of liver disease stage and tests before and on HCV-specific therapy are summarized in Table 2.

The proposed management algorithm for PEG-IFN- α and RBV combination therapy in HIV/HCV-coinfected individuals is shown in Fig. 3. Recent data from the Peginterferon Ribavirin España Coinfección (PRESCO) trial clearly favour higher RBV doses than the 800 mg/daily dose of RBV used in the AIDS Pegasys Ribavirin Coinfection Trial (APRICOT) and RIBAVIC trials [10–12]. Moreover, the PRESCO trial indicates that at least some patients may benefit from a longer duration of HCV combination therapy of up to 72 weeks (see Fig. 3). More recent data also suggest that patients infected with genotype 2/3 with low viral loads (<400 000 IU/mL) and mild fibrosis who achieve an undetectable HCV RNA by 4 weeks (rapid virological response) may only need 24 weeks of therapy [13]. Patients with a history of previous HCV therapy who were either nonresponders or relapsed under previous HCV therapy need to be reassessed with regard to a new HCV treatment, optimizing dose and duration as well as providing the best possible supportive therapy. Table 3 summarizes possible interventions for HCV/HIV-coinfected nonresponders and relapsers to prior interferon-based therapies.

Conclusions

With the introduction of new medications for treatment of HBV infection, therapeutic options for HIV/HBV-coinfected patients have improved considerably. Complete suppression of HBV replication in an HIV/HBV-coinfected patient with an indication for therapy appears to be crucial in order to prevent resistance development.

Individualized HCV therapy seems to be the best approach to maximize treatment success and minimize HCV therapy-related toxicities. As new drugs for HCV therapy will not become available within the very near

future, all HIV/HCV-coinfected patients should at least be evaluated for the current treatment paradigm, as HCV can be eradicated in almost half of patients who undergo combination HCV therapy.

General statement

The hepatitis coinfection guidelines will be updated as new evidence emerges – please check on www.eacs.ws for the most recent version. Conflict-of-interest statements from all panel members also appear on this website.

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