JUST SAY NO TO TEST AND TREAT FOR HBV

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CONFLICTS OF INTEREST

- Our Program has 2 research grants from Gilead Sciences neither of which funds any of our salaries

THE PROS AND CONS OF EVIDENCED-BASED GUIDELINES

- Pros:
  - Use an accepted format such as PICO (Population, intervention, comparison, outcome)
  - For each recommendation, grade the quality of evidence (e.g. randomized-controlled trial vs. case series) and recommendations are scored for the strength of the recommendation
    - This helps clinician estimate likelihood intervention will be of benefit to patient
  - Strong attempt to eliminate or minimize bias
  - Still allow clinician to make the final decision about treatment (Guidelines, not Standards of Care)
- Cons: Information is usually incomplete if critical publish data are not available or quality data is lacking
- Often times they are too narrow so that patients who might benefit from treatment may not be included due to lack of evidenced-based data to make recommendations

WHAT IS THE TEST AND TREAT STRATEGY?

- Test all persons in a population for HBsAg and put all persons positive on tenofovir for life
- Cost per year: Initial cost $1 for rapid HBsAg test
  - $48-$72/year for TDF or TAF
  - No further testing or follow-up costs, but yearly drug costs continue
- Downsides:
  - Many patients will not need treatment as they would be in the inactive phase of HBV normal ALT and HBV DNA <1,000 to 2,000 IU/ml or even not detectable
  - Patients may not take medication regularly: very common occurrence that we see in Alaska
    - By monitoring ALT and HBV DNA, we can often tell when patients quit taking their antiviral
    - No big deal if in the inactive phase without cirrhosis, but flares of HBV could occur 2-4 weeks after stopping in those in the immune active phase
      - In patients with cirrhosis, this could result in liver failure
    - Long-term risk of renal and bone side effects: Low but risk is still there

WHAT ARE OTHER CONCERNS ABOUT TEST AND TREAT APPROACH

- Test and treat less likely to be of benefit for persons in the inactive phase of HBV
  - Except in areas where genotype C predominates 75% of persons over 30 years are likely to be HBeAg-negative (Livingston SE, Gastroenterology 2007;133:1452-57)
    - In a study following 754 patients who were HBeAg-negative, 25% meet AASLD criteria for treatment over an 8-year period;
      - Of those 55% initially and 45% during follow-up (McMahon BJ et al Clinical Gastroenterol and Hepatology 2014;12:701-706
    - In a subset who were in the inactive phase at entry (normal ALT & HBV DNA < 2,000 IU/ml), the incidence of reactivation (HBV DNA>2,000 IU/ml and elevated ALT) was only 1.2%/year over a 7.4 year period (Tomhe, RA et al. J Clinic Virology 2013;58:396-400)
    - Viral reactivation was significantly more frequent in those with HBV DNA > 1,000 IU/ml

CONCERNS CONTINUED

- Persons in the inactive phase have a strong immune response that keeps the virus suppressed and may help protect against HCC. Removing this response is of no benefit immediately to the patient and might be harmful in the long run, though this has never been studied
- Thus if in addition to HBsAg, HBV DNA were done at time of screening, then a better capture of who might benefit the most would be done

THE CASE FOR HBV DNA TESTING

- HBV DNA testing using GeneXPert ranges from $12 to $14/ cartridge.
  - Testing can be performed with a finger stick
  - The Global Fund has provided the GeneXPert platform most large and medium sized hospitals in Low and Middle Income Countries
  - Cost on one HBV DNA test is less expensive than one year of tenofovir (~$14 vs. vs. $48-$72)
    - Add cost of HBsAg by fingerstick once yearly, add $1
      - TDF could be stopped for persons who clear HBsAg
      - For those in the inactive phase not on TDF, 1% to 2% will lose HBsAg/year and unless treatment for HCC is available, then these patients may not need further testing
  - Cost of treating 100 patients with only a baseline HBsAg/year vs. cost of treating 25 to 50 patients with elevated HBV DNA at baseline (assuming no more than 50% would have elevated HBV DNA and ALT)

COST OF CARING FOR 100 PATIENTS USING TEST AND TREAT VS. TREAT ONLY IF HBV DNA AND ALT ARE ELEVATED

- Test and Treat:
  - First year: $1 for HBsAg plus $50 for TDF: $51: For 100 patients $5,100
  - Subsequent years $50/year for TDF, no testing cost; cost per 100 patients $5,000/year
- Treat only if HBV DNA >2,000 IU/ml and ALT abnormal at baseline
  - First year: $1 for HBsAg, $15 for HBV DNA equals $16/patient and $50 if treated with TDF: $66/patient
    - If 25% qualify for treatment: $16/patient for testing: $1,600 testing/$1250 for TDF=$2850 for 1st year
    - If 50% need treatment: $16+$50 for TDF=$66/patient: cost/100 patients $1,600 testing/$2,500 for TDF equals $4,100 for 1st year
    - Cost for HBsAg+ patients with HBV DNA < 2,000 IU/ml: $1,600/year for HBV DNA and $1 for HBsAg ($1,700/year)
  - Subsequent years:
    - Same as above minus $1 for Test and treat: $5,000/year
    - Treat of ALT and HBV DNA elevated: same as first year costs above

EVALUATION OF THE TEST AND TREAT STRATEGY VS. TREATING ONLY IF ALT AND HBV DNA IS ELEVATED

- Test and Treat Strategy
  - Baseline incidence of HBV related liver failure and HCC
  - Five and 10-year follow-up on the incidence of liver failure and HCC
  - This requires setting up a surveillance system
  - Without a well designed study to evaluate the effectiveness of test and treat, it will be difficult to justify expanding this program to other countries
- Treat using laboratory criteria
  - Evidence-based reviews by WHO and AASLD contracted experts have shown that treating patients meeting the criteria reduces the incidence of liver failure and HCC with the strongest effect on potentially eliminating liver failure
  - Though documenting the incidence of liver failure and HCC such a vigorous evaluation study may not be necessary

OTHER APPROACHES THAT COULD BE TRIED

- Baseline testing for HBsAg and HBV DNA with a longer interval for follow-up
  - Yearly for those on antiviral therapy for the first few years then less frequently for those whose HBV DNA levels are normal subsequently could cut cost of testing
  - Test and treat strategy using baseline HBsAg and HBV DNA for those positive:
    - Placing only those HBsAg positive with HBV DNA > 2,000 IU/ml, elevated ALT on TDF with either:
      - No subsequent follow-up laboratory testing (enhanced test and treat strategy)
      - Staggered follow-up and lab testing at one year vs. 2 years vs. 3 years
    - For persons HBsAg-positive with HBV DNA <2,000 IU/ml: yearly follow-up
      - Follow-up HBV DNA only on those with baseline level >1,000 IU/ml with yearly HBV DNA and ALT (see reference slide 5)
      - Follow-up those with HBV DNA <1,000 IU/ml with only ALT and HBsAg every 1-3 years

WHERE SHOULD WE PUT OUR EFFORTS INSTEAD OF TEST AND TREAT

- Birth dose. < 50% of newborns receive the birth dose
  - Cost is 30 to 50 cents/dose
  - All countries should strongly consider implementing the birth dose for babies born in hospitals and clinics while planning how to do this nationally and delaying the easy ones to catch
- Working with HIV colleagues to bundle hepatitis B and C screening when HIV screening is done
  - Offering treatment to HCV infected patients
  - Linking HBV DNA patients to care
    - HIV clinics have personnel who are experts at caring for persons with chronic viral infections

CONCLUSIONS

- Now that the cost of HBV DNA testing has come down and is more readily available and could fall further.
- Test and Treat strategy without incorporating HBV DNA could be more costly over the long run
  - Many patients in the inactive phase would be treated and there could be a downside of potentially turning off their potent immune response to the virus
  - Patients who stop or intermittently take their meds could have flares of HBV that could be catastrophic if they have underlying cirrhosis
  - Though bone and renal side effects are uncommon, a small percentage of patients would be expected to suffer these consequences. This could be avoided if those in the inactive phase were not treated
  - Long-term outcomes of test and treat would need to be performed to justify expanding to other nations