Question: Should routine two-dose* vaccination to prevent hepatitis A virus infection be given to HIV-positive persons?
Population: Adult HIV-positive persons
Intervention: Routine two-dose* hepatitis A vaccination
Comparison(s): No routine two-dose* hepatitis A vaccination
Outcomes:

- Hepatitis A infection
- Mild adverse events
- Serious adverse events

*Or three-dose vaccination when a combination vaccine is used.

Background:

In 2015, there were an estimated 1.12 million persons with HIV (PWHIV) in the United States (*1*). When PWHIV are co-infected with hepatitis A virus (HAV), they experience higher peak HAV viral loads and a prolonged duration of hepatitis A viremia compared to persons without HIV infection, and are therefore more likely to transmit HAV. HAV co-infection may increase HIV viral load, potentially also increasing HIV transmission. PWHIV respond to hepatitis A (HepA) vaccine with seroconversion rates of 48.5%–94.0% (*2,3,4*) following a 2-dose monovalent vaccination schedule; factors associated with a protective antibody response in PWHIV include a CD4+ cell count above 200/µl and a low HIV RNA viral load.

The Advisory Committee on Immunization Practices (ACIP) currently recommends HepA vaccine for groups at increased risk of HAV or severe HAV infection, but does not specify PWHIV as a risk group. The groups currently indicated for HepA vaccine include persons traveling to or working in countries that have high or intermediate endemicity of infection, men who have sex with men (MSM), persons who use injection or non-injection drugs, persons with clotting-factor disorders, persons who have occupational risk for infection, persons who anticipate close personal contact with an international adoptee, persons with chronic liver disease, and persons experiencing homelessness. The Medical Monitoring Project (*5*), which samples PWHIV in the United States and collects clinical and behavioral information, estimates that 59.9% *(*95% CI: 57.3–62.4) of PWHIV had one of the following indicators: male-to-male sexual contact in the past 12 months, injection or non-injection drug use in the past 12 months, experiencing homelessness in the past 12 months, chronic liver disease, or a clotting factor disorder. Data were not available for proportions of PWHIV who have occupational risk for infection, who travel, or who have close contact with an international adoptee; excluding these groups, 40.1% (95% CI: 37.6–42.7%) of PWHIV in the United States do not have a known ACIP-recommended indication for HepA vaccine.

From January 2017 to February 2019, more than 12,500 cases of HAV infection in the United States were associated with person-to-person transmission in multiple states. HIV co-infection data are available for these cases from a limited number of

states. Among 249 reported HAV cases in Tennessee, 11 (4%) patients were PWHIV (*6*). Six (55%) of these 11 HAV/HIV co-infected patients received partial or complete HepA vaccination prior to acute hepatitis A infection. There were no identified cases of breakthrough acute hepatitis A infection in previously vaccinated persons not infected with HIV. The data from Tennessee and reports from other HAV outbreak–associated states indicate a need to include PWHIV as an indication for HepA routine vaccination, and potentially for additional prophylaxis after a potential exposure to HAV.

Additional background information supporting the ACIP recommendations on the use of HepA vaccine can be found in the relevant publication of the recommendation referenced on the ACIP website.

	CRITERIA	WORK GROUP JUDGMENTS	EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem of public health importance?	*No* ☐ *Probably no* ☐ *Uncertain* ☐ *Probably yes* ☐ *Yes* ☒ *Varies* ☐	▪ PWHIV are at increased risk of HAV infection. – HIV infection leads to an immunocompromised state – PWHIV are frequently less likely to be vaccinated for a variety of reasons (missed opportunities for vaccination, lack of access to health care, etc.). ▪ Outbreaks that include PWHIV can have prolonged HAV transmission. – HAV viremia in PWHIV tends to be higher and more durable. • In 2015, there were an estimated 1.12 million PWHIV in the United States (*1*). • HIV co-infection outbreak data are available for a limited number of states. o Among 249 reported cases of hepatitis A in Tennessee, 11 (4%) patients were PWHIV (*6*).	▪ Infectious Diseases Society of America recommends vaccinating all PWHIV against HAV infection as part of their guidelines (*9*). Eleven other manuscripts described routinely vaccinating PWHIV as part of clinical practice (*10–20*). ▪ Spain, Italy, and Australia report routinely vaccinating all PWHIV against HAV infection.

			○ Among 359 reported cases of hepatitis A in Massachusetts, 4% were PWHIV (as of June 5, 2019) (*7*). ○ Among 85 reported cases of hepatitis A in Illinois, 7 (8.2%) were PWHIV (as of June 5, 2019) (*8*).	
BENEFITS & HARMS	How substantial are the desirable anticipated effects?	*Minimal* ☐ *Small* ☐ *Moderate* ☐ *Large* ☒ *Don't know* ☐ *Varies* ☐	▪ HAV infection may increase HIV replication, potentially increasing potential for HIV transmission. ▪ HAV viremia in PWHIV tends to be higher, more durable, and can lead to a longer transmission period. ▪ HepA vaccine is a highly effective vaccine in the general population. – Seroconversion rates in PWHIV are 48.5%–94% (*2*–*4*). Higher rates of response among PWHIV to vaccination were associated with higher baseline median CD4+ count at vaccination and/or lower HIV viral load.	
	CRITERIA	WORK GROUP JUDGMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
	How substantial are the undesirable anticipated effects?	*Minimal* ☒ *Small* ☐ *Moderate* ☐ *Large* ☐ *Don't know* ☐ *Varies* ☐	▪ Over 20 years of safety monitoring have shown no safety concerns (CDC, unpublished). ▪ Similar rates of serious adverse events have been observed in PWHIV vs. HIV-negative persons. – No unexpected vaccine adverse events were reported	

			among PWHIV from 1990 to 2016. ▪ HepA vaccine does not increase HIV viral load or CD4+ cell count, nor does it speed progression to AIDS.	
	Do the desirable effects outweigh the undesirable effects?	*Favors intervention* ☒ *Favors comparison* ☐ *Favors both* ☐ *Favors neither* ☐ *Unclear* ☐	▪ Although seroconversion rates among PWHIV are lower following vaccination compared to the HIV-negative population, seroprotection against HAV infection in PWHIV can be achieved. ▪ Out of 130 PWHIV, 89% maintained seropositivity 6–10 years after a two-dose vaccine series (*21*). – Vaccination at higher CD4+ counts is associated with better vaccine-induced immune response.	
	What is the overall certainty of this evidence for the critical outcomes?	Effectiveness of the intervention *No included studies* ☐ *4 Very low* ☐ *3 Low* ☐ *2 Moderate* ☒ *1 High* ☐ Safety of the intervention *No included studies* ☐ *4 Very low* ☐ *3 Low* ☒ *2 Moderate* ☐ *1 High* ☐	Please refer to GRADE (safety and effectiveness) tables for detailed assessment of the certainty of the evidence. For more information, please see the ACIP Handbook for Developing Evidence-Based Recommendations. • The benefit outcome, reduction in hepatitis A infection, among randomized controlled trials (RCTs) was graded as EVIDENCE TYPE 2. • We downgraded for indirectness due to variability of hepatitis A antibody	Due to these vaccines' long-term safety record, and lack of any significant adverse safety signal in the Vaccine Adverse Event Reporting System or in the literature, the workgroup was confident in the safety of this vaccine in this population.

			seroconversion thresholds used.
			• The benefit outcome, reduction in hepatitis A infection, among observational studies was graded as EVIDENCE TYPE 4.
			  • We downgraded for indirectness due to variability of hepatitis A antibody seroconversion thresholds used and for risk of bias due to limited studies comparing a 2-dose standard intervention to no vaccine.
			• The harm outcome, mild adverse events, among RCTs was graded as EVIDENCE TYPE 1.
			• The harm outcome, mild adverse events, among observational studies was graded as EVIDENCE TYPE 3.
			• The harm outcome, <u>serious adverse events</u>, among RCTs was graded as EVIDENCE TYPE 3.
			  • We downgraded for very serious imprecision due to small study population size.
			• The harm outcome, serious adverse events, among observational studies was graded as EVIDENCE TYPE 4.
			  • We downgraded indirectness for use of multiple non-hepatitis A vaccines and for	

			imprecision due to small study population size.	
VALUES	Does the target population feel that the desirable effects are large relative to undesirable effects?	*No* ☐ *Probably no* ☐ *Uncertain* ☐ *Probably yes* ☒ *Yes* ☐ *Varies* ☐	▪ Few studies have been conducted to investigate PWHIV preferences regarding HAV infection. ▪ Reasons for non-vaccination (*22*): – Not recommended by providers – Lack of expected effectiveness – Fear of vaccine adverse effects	
	CRITERIA	WORK GROUP JUDGMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
	Is there important uncertainty about or variability in how much people value the main outcomes?	*Important uncertainty or variability* ☐ *Possibly important uncertainty or variability* ☐ *Probably no important uncertainty or variability* ☒ *No important uncertainty or variability* ☐ *No known undesirable outcomes* ☐	• Few studies have been conducted specifically to determine the value PWHIV assign to protection against HAV. • Among people who use injection drugs from five U.S. cities (24.2% of whom were PWHIV) (*23*), convenience was the important determining factor for initiating HepA/hepatitis B (HepB) vaccination.	
ACCEPTABILITY	Is the intervention acceptable to key stakeholders?	*No* ☐ *Probably no* ☐ *Uncertain* ☐ *Probably yes* ☐ *Yes* ☒ *Varies* ☐	▪ The proposed recommendation parallels ACIP recommendations for HepB vaccination in PWHIV. – Similarly lower seroresponses have been observed after HepB vaccine administration among PWHIV with low CD4+ counts. ▪ ACIP currently recommends that all HIV patients receive their first dose of HepB vaccine during their first	

			HIV care visit after having their hepatitis B virus serologies drawn. – This option is safe and effective for PWHIV and less confusing for providers.	
RESOURCE USE	Is the intervention a reasonable and efficient allocation of resources?	*No* ☐ *Probably no* ☐ *Uncertain* ☒ *Probably yes* ☐ *Yes* ☐	▪ Adult HepA vaccines are licensed only for certain high-risk groups, and cost effectiveness data on vaccine use for these indications are limited. ▪ Outbreaks and subsequent response efforts incur medical costs, productivity losses, disruption of other public health services, and diversion of public health resources and extensive human resources. – Cost of an outbreak among people who use injection drugs (n = 590, Washington): $3.3 million (*24*). – Cost of an outbreak among MSM (n = 136, Ohio): $520,039 (*24*). – The cost of routine immunization through HIV and primary care clinics may be lower per capita than the cost of large, rapid vaccination campaigns for outbreak response.	A true cost-effectiveness analysis has not been performed.

FEASIBILITY	Is the intervention feasible to implement?	*No* ☐ *Probably no* ☐ *Uncertain* ☐ *Probably yes* ☒ *Yes* ☐ *Varies* ☐	▪ Vaccine response improves if individuals are vaccinated earlier in the course of HIV infection, when they tend to have higher initial CD4+ counts and lower HIV RNA viral loads. ▪ Despite existing recommendations to vaccinate based on specific risk factors, there is inadequate screening and vaccination for HAV among PWHIV, even in HIV clinics. – In a US study, 23.3% of eligible outpatient PWHIV received 1 dose of HepA vaccine (*25*). – In a British study, HepA vaccine was indicated in 75% of PWHIV, but had been delivered to only 36% of eligible individuals (*26*).	Simplifying provider guidance may improve protection of at-risk PWHIV.

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐	Undesirable consequences *probably outweigh* desirable consequences in most settings ☐	The balance between desirable and undesirable consequences *is closely balanced* or *uncertain* ☐	Desirable consequences *probably outweigh* undesirable consequences in most settings ☒	Desirable consequences *clearly outweigh* undesirable consequences in most settings ☐	There is insufficient evidence to determine the balance of consequences ☐

Is there sufficient information to move forward with a recommendation?

Yes ☒ No ☐

Policy Options for ACIP Consideration	ACIP does not recommend the intervention ☐	ACIP recommends the intervention for individuals based on shared clinical decision-making ☐	ACIP recommends the intervention ☒
Recommendation (text)	All persons with HIV aged 1 year and older should be routinely vaccinated against hepatitis A.		
Additional considerations (optional)			

Final deliberation and decision by the ACIP

Final ACIP recommendation	ACIP does not recommend the intervention ☐	ACIP recommends the intervention for individuals based on shared clinical decision-making ☐	ACIP recommends the intervention ☒
ACIP considerations	All persons with HIV aged 1 year and older should be routinely vaccinated against hepatitis A.		

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