Use of Hepatitis A Vaccine for Persons With HIV – GRADE and Evidence Tables

Evidence Retrieval

- For evidence retrieval, we conducted a systematic review of data on hepatitis A vaccine and persons with HIV (PWHIV), including searches of Medline, EMBASE, CINAHL, Cochrane Library, and ClinicalTrials.gov through January 17, 2019.
- Our search terms were as follows:
  (((Hepatitis OR HAV OR hepatovirus) AND vaccin*) OR HepA OR VAQTA OR AVAXIM OR EPAXAL OR HAVPUR OR HAVRIX OR nothav) AND (HIV OR human immunodeficiency)
- We did not restrict articles based on language or country of origin.

We excluded articles based on the following criteria:

- Articles focused solely on children or that did not have information on ages of included individuals
- Articles with no data on HAVRIX or VAQTA, which are the two single-antigen hepatitis A vaccines currently licensed in the United States
- Articles that did not provide new data, only included safety data among populations other than our target population of PWHIV, discussed vaccine introduction, made recommendations, or proposed guidelines
- Articles that could not be obtained full-text or in English
- Articles on animals other than humans
- Clinical trials with no results available
- Publication prior to 1996, when hepatitis A vaccine was introduced in the United States

- We identified 927 unique abstracts; 584 abstracts met one or more of the exclusion criteria (above), leaving 343 articles for full-text review.
- Based on review of the full publications, we eliminated another 319 articles per exclusion criteria. We also excluded 2 studies with populations that were a subset of other included studies.
- We included a total of 22 studies in our GRADE analysis.

GRADE of evidence for hepatitis A vaccination among persons living with HIV: Benefits*

Outcome #1: Hepatitis A infection

Study	Type	Site	Population N = total	Age	Intervention	Comparison	CD4+ Count at Vaccination	HIV Viral Load at Vaccination	Immunogenicity*	Main Outcomes #1
Lin, 2018	Obs	Taiwan	N = 1533	Median, vaccinated group: 35	At least 1 dose of HAV vaccine		Median, cells/lL: 550		Weeks 28–36: 63.8% (ITT) and 93.7% (PPA)	Vaccine effectiveness: 96.3%
Cheng, 2017	Obs	Taiwan	N = 365	Mean: 30	HAVRIX, 2 doses at 0, 6 months; HAVRIX, 3 doses 0, 1, 6 months		Mean: 485 cells/mm^3		Primary responders: 87.3% (2 dose) 88.9% (3 dose)	GMCs‡ of anti-HAV immunoglobulin G (IgG): significantly higher for 3-dose versus 2-dose
Tsachouridou, 2017	Obs	Greece	N = 1210	Mean: 34.51	HAVRIX, 2 doses at 0, 6–12 months; ENGERIX, 3 doses at 0, 4, and 24 weeks; PNEUMOVAX 23		Mean: 2.70 log10	Mean, log10 copies/ml: 4.18	80.7% seroconversion within 3 months of HepA series completion	Seroprotection not affected by nadir and current CD4+ cell count and plasma viral load
Jablonowska, 2014	Obs	Poland	N = 234	Mean age, vaccinated: 30.7	HAVRIX, 2 doses, 6 months apart		Median: 450 cells/mm^3		79.5%, one month after second dose 75.5%, 5 years after vaccination	Most HIV-infected adults with high CD4+ counts had a durable response up to 5 years post vaccination
Kourkounti, 2014	Obs	Greece	N = 897	Mean, vaccinated group: 40.2	HAVRIX or VAQTA, 2 doses, 6-12 months apart				Response rate: 76%	GMT‡: 305 mIU/ml (95% CI 255-361 mIU/ml)
Jimenez, 2013	Obs	USA	N = 226	Mean: 41.8	At least 1 dose: a) HAVRIX b) TWINRIX (720 EU)		Median: 410 cells/mm^3	Median: 1287 copies/mL	53.5% overall 54% (HAVRIX) 53% (TWINRIX)	Patients with CD4+ counts >350 cell/mm^3 (60%) were more likely to respond than those with CD4+ counts <200 cell/mm^3 (35%) (P = 0.0498). Responders were also more likely to be virologically suppressed (48% versus 32%; P = 0.0024).

Kourkounti, 2013	Obs	Greece	N = 113	Median: 40	HAVRIX or VAQTA, 2 doses, 6–12 months apart		Median, cells/mm^3: 570	Median, copies/mL: <50	After the second dose: 77.0%	GMT‡: Highly active antiretroviral therapy (HAART) patients, 237 mIU/mL [95% CI, 201–321 mIU/mL]; no HAART, 158 mIU/mL [95% CI, 130–221 mIU/mL]), *P* = 0.068
Mena, 2013	Obs	Spain	N = 499	Median: 36.3	(a) HAVRIX, 1 dose (b) HAVRIX, 2 doses, 6 months apart (c) TWINRIX (720 EIU), 3 doses at 0,7,14–21 days		Median, cells/mm^3: 531, standard schedule 543, rapidly accelerated	Median, log10 copies/ml: 2.3	Overall rate: 73.4% (a) 60.0% (b) 80.7% (c) 70.7%	Protective antibody response to vaccination was associated with a higher CD4+/CD8 ratio. Higher response was associated with reception of 2 doses of standard schedule (in comparison with those receiving only one of those of the same schedule)
Tseng, 2013	Obs	Taiwan	N = 582 (365 HIV+)	age range: 18–40	(a) HAVRIX, 2 doses at 6 months apart (b) HAVRIX, 3 doses at 0, 1, and 6 months	(c) HAVRIX, 2 doses at 6 months apart (HIV- group)	Mean, cells/mm^3: (a) 538 (b) 452	(a) 2.5 log10 copies/mL (b) 3.0 log10 copies/mL	Week 48 (ITT**): (a) 75.7% for 2-dose HIV+ (b) 77.8% for 3-dose HIV+ (c) 88.5% for 2-dose HIV-	GMC‡ at week 48 (*P* <0.01): (a) 2-dose, 1.94 log10 mIU/mL (b) 3-dose, 2.29 log10 mIU/mL Protective antibody response associated with higher CD4+ counts and undetectable plasma HIV RNA load.
Kourkounti, 2012	Obs	Greece	N = 351	Median: 40 (range 34–45)	HAVRIX or VAQTA, 2 doses, 6–12 months apart		Median: 564 cells/mm^3	60% had <50 copies/mL at or prior to dose 1 HAV	1 month after the second dose: 74.4% GMTs: 315, 203, 153, and 126 mIU/ml at months 1, 6, 12, and 18	A higher response rate and higher GMTs were observed in patients with CD4+ counts ≥500 cells/mm^3 (76.6%) than in patients with CD4+ counts 200–499 cells/mm^3. Protective antibody response to vaccination was associated with higher baseline median CD4+ count at vaccination.
Weinberg, 2012	Obs	USA	N = 373	Mean: - responders: 41.7 - non-responders: 41.6	HepA (unspecified 2 dose vaccine 6 months apart or 3 dose vaccine every 2 months)		Mean, cells/μl: responders: 519 non-responders: 450	Plasma HIV RNA <400 copies/ml: responders: 46% non-responders: 35%	52% in HAV-seronaïve	Plasma HIV RNA <400 copies/ml, higher CD4+ cells/μl, and baseline antibody titers <20 mIU/ml (HAV seronaïve) were significantly associated with an antibody response to the vaccine
Crum-Cianflone, 2011	Obs	USA	N = 130	Median: 35	VAQTA or HAVRIX, 2 doses, 6–18 months apart	Controls: HIV-negative, VAQTA, 2 doses	Median: 461 cells/mm^3	Plasma HIV RNA level, <1000 copies/mL: 49%	89% overall 78%, CD4+ <350 cells/mm^3 94%, CD4+ ≥350 cells/mm^3	GMCs‡ among HIV+ adults: 154, 111, and 64 mIU/mL at 1, 3, and 6–10 years. Higher GMCs over time among HIV-infected adults were associated with lower log10 HIV RNA levels (*P* = 0.04)

Armstrong, 2010	Obs	USA	N = 451	Mean: 40	HepA (standard dose) or HepB (standard dose) or TWINRIX		64%, CD4+ >400 cells/mm^3 36%, CD4+ ≤400 cells/mm^3		HepA: 60%, overall 62.5%, CD4+ >400 55.56%, CD4+ ≤400	Immune development to HepA increased as CD4+ counts increased
Horster, 2010	Obs	Germany	N = 131	Mean: 40	HAVRIX, 2 doses at months 1 and 6 or TWINRIX (720 EU), 3 doses at months 1, 3, 6; plus additional vaccines***		Median: 423.0 CD4+/µl	Median: below limit of detection	63.6%	Seroconversion was 63.6% among those receiving hepatitis A vaccine
Launay, 2008	RCT	France	N = 99	Mean: 38.8 years	HAVRIX, 2 doses, 24 weeks apart	HAVRIX, 3 doses at weeks 0, 4, 24	Median, cells/mm^3: 355	Median, copies/mL (IQR): <50 (<50–1300)	Week 28, ITT**: 69.4%, 2-dose group 82.6%, 3-dose group (P = 0.13)	GMT‡, mIU/mL: 138.2, 2-dose vs. 323.5, 3-dose group at 28 weeks
Overton, 2007	Obs	USA	N = 906	Mean, vaccinated group: 38.1	HAVRIX, at least 1 dose		Mean, cells/mm^3: 447		49.6% overall	Protective antibody response to vaccination with HIV viral RNA load <1000 copies/ml
Weissman, 2006	Obs	USA	N = 503	Mean: - responders, 43.5 - non-responders, 45.0	HAVRIX, 2 doses, 6–12 months apart		Mean, cells/mm^3: overall: 424 responder: 508.6 non-responder: 344.3		After the 2nd dose (mean of 187 days post series completion): 48.5%	Protective antibody response to vaccination was associated with higher CD4+ count
Rimland, 2005	Obs	USA	N = 659	Age not published	HAVRIX, 2 doses				After the 2nd dose: 60.7%	Protective antibody response to vaccination was associated with higher CD4+ count, especially if >200 cells/mm^3
Wallace, 2004	RCT	USA	N = 180 (90 HIV+)	Mean: 32.6 years	VAQTA, 2 doses, week 0 and week 24	Placebo	Mean, cells/mm^3: 457.5, VAQTA 493.6, placebo	Mean, copies/mL: 0.33 x 10^5, VAQTA 0.16 x 10^5, placebo	Week 28: 94% among HIV-infected subjects 87%, CD4+ <300 cells/mm^3 100%, CD4+ ≥300 cells/mm^3	GMT‡, mIU/mL: 517 subjects with CD4+ <300 cells/mm^3; 1959 subjects with ≥300 cells/mm^3

Kemper, 2003	RCT	USA	N = 133	Mean: 38 years	HAVRIX, 2 doses, 6 months apart	Placebo, 2 doses, 6 months apart	Mean, cells/mm^3: - 376, vaccine - 327, placebo (*P*, not significant)	Mean, log_{10} copies/mL: 3.2, vaccine 3.39, placebo	Month 9: 68%, CD4+ ≥200 cells/mm^3 9%, CD4+ <200 cells/mm^3 (*P* = 0.004)	Protective antibody response to vaccination was significantly associated with CD4+ cell counts ≥200 cells/mm^3
Lederman, 2003	Obs	USA	N = 643	Median: 40	HAVRIX, 2 doses, weeks 16 and 40 + multiple antigens****		Median, cells/mm^3: 226	Median copies/mL: ≤500	8 weeks after second dose: 46%	46% of subjects seroconverted after 2 doses of hepatitis A vaccine
Valdez, 2003	Obs	USA	N = 38	Median: 38	HAART and IL-2 vaccinated with: HAVRIX + tetanus toxoid + REMUNE + ENGERIX	HAART-only vaccinated with: HAVRIX + tetanus toxoid + REMUNE + ENGERIX	Median, cells/µL: HAART/IL-2: 865 HAART: 445	Median, log10 copies/mL (IQR): HAART/IL-2: 1.7 (1.7 - 2.6) HAART: 1.7 (1.7 - 1.7)	88% of HAART-only recipients 36% of HAART/IL-2 recipients	Seroconversion was 88% among HAART-only and 36% among HAART/IL-2 groups

‡GMT/ GMC: geometric mean titer/geometric mean concentration

* Seroconversion defined as anti-HAV antibody concentrations:
  - ≥10 mIU/ mL: Horster; Wallace
  - ≥10 mIU/ mL at 12 (±6) months after second dose: Crum-Cianflone
  - ≥20 mIU/mL: Kourkounti, 2012; Kourkounti, 2013; Kourkounti, 2014; Mena; Tsachouriou; Weinberg; Tseng; Launay; Jablonowska
  - Primary responders: ≥20 mIU/mL at month 12: Cheng
  - ≥33 mIU/mL: Kemper

** ITT: Intention to treat analysis.

*** Additional vaccines administered: trivalent influenza split-vaccine (INFLUSPLIT), pneumococcal vaccine (PNEUMOVAX 23), hepatitis B (ENGERIX; administered at months 1, 3, if HAVRIX given for hepatitis A).

**** Antigens included *Candida albicans*, mumps skin test, and TT US Pharmacopeia fluid; tetanus toxoid vaccine was also administered unless previously received in past 12 months.

GRADE of evidence for hepatitis A vaccination among persons living with HIV: Harms
Outcome #2: Mild adverse events

Study	Type	Site	Population N = total	Age, years	Intervention	Comparison	Main Outcomes #2
Kemper, 2003	RCT	USA	N = 133	Mean: 38	HAVRIX, 2 doses, 6 months apart	Placebo, 2 doses, 6 months apart	Minor injection site soreness: 35% of vaccine doses administered versus 8% of placebo doses (*P* <0.01). Reported bacterial, viral, or fungal infections post-vaccination similar for patients receiving vaccine or placebo (24% vs. 26%, respectively; *P* >0.20). Within 4 days of vaccination, 1 subject (1.6%) in each group experienced severe headache; 1 subject (1.6%) in vaccine group experienced severe fatigue. This difference was non-significant. We consider these to be relatively mild adverse events. The authors concluded that the vaccine was well tolerated in this population.
Wallace, 2004	RCT	USA	N = 180 (90 HIV+)	Mean: 32.6	VAQTA, 2 doses, week 0 and week 24	Placebo	Local reaction at injection site in 57% of VAQTA group and 60% of placebo group. Systemic adverse events (predominantly self-limited headache and fever) were more common among PWHIV who received VAQTA (37%) than among PWHIV who received placebo (23%). Only 3 subjects experienced clinically significant adverse events within 2 weeks after receipt of either vaccine dose. Only 1 of these 3 events (a severe headache) was thought to be vaccine-associated. There were no significant changes in complete blood counts or the results of liver function tests in any group at any point in this study.

Tseng, 2013	Obs	Taiwan	N = 582 (365 HIV+)	range: 18–40	HAVRIX, 2 doses, 6 months apart	HAVRIX, 3 doses at 0,1 and 6 months	51.6% of all subjects (HIV+ 51.7% vs HIV- 51.6%, *P* = 0.98) experienced mild tenderness at local injection site within 24 hours of vaccination.

Outcome #3: Serious adverse events

Study	Type	Site	Population N = total	Age	Intervention	Comparison	Main Outcomes #2
Launay, 2008	RCT	France	N = 99	Mean: 38.8	HAVRIX, 2 doses, 24 weeks apart	HAVRIX, 3 doses at weeks 0, 4, 24	There were no serious adverse events associated with the vaccine. No significant changes in CD4+ T-cell counts or plasma HIV-1 RNA levels during 28-week follow-up.
Bodsworth, 1997	Obs	Australia	N = 180	Mean: - case: 33.2 - control: 36.6	HAVRIX, 2 doses at 1 or 6 months apart	No vaccine for controls	No significant differences (*P* >0.2) between case and control groups after 1 year for: - AIDS progression, 10.1% versus 10.7% - Death, 7.3% versus 7.6% - Mean CD4+ decline, 125 x10^6/l versus 123 x10^6/l No serious adverse events attributable to vaccination.
Wallace, 2004	RCT	USA	N = 180 (90 HIV+)	Mean: 32.6	VAQTA, 2 doses, week 0 and week 24	Placebo	No adverse effect on either HIV viral load or CD4+ cell count found.

***RCT – randomized control trial**
Obs – observational study
GMT – geometric mean titer
GMC – geometric mean concentration
ITT- intention to treat

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