Utility of novel viral and immune markers in predicting HBV treatment endpoints: A systematic review of treatment discontinuation studies

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Table S1: International Guidelines on HBV Treatment Cessation

	International Guidelines on HBV Treatment Cessation *(In absence of HBsAg loss)*
APASL (2015)	
HBeAg+ populations	HBeAg seroconversion & at least 1-3 years of consolidation therapy following virological suppression
HBeAg- populations	At least 2 years of treatment & 1 year of consolidation therapy following virological suppression (tested 3 times, 6 months apart)
Follow-up	Follow-up monthly for first 3 months, then every 3-6 months indefinitely
EASL (2017)	
HBeAg+ populations	HBeAg seroconversion & at least 6-12 months of consolidation therapy following virological suppression
HBeAg- populations	At least 3 years of consolidation therapy following virological suppression
Follow-up	Close post-NA therapy monitoring required
AASLD (2018)	
HBeAg+ populations	HBeAg seroconversion & at least 12 months of consolidation therapy following virological suppression
HBeAg- populations	Indefinite treatment unless compelling rationale
Follow-up	Follow-up every 3 months for at least 1 year

Abbreviations: AASLD: American Association for the Study of Liver Diseases, APASL: Asian Pacific Association for the Study of the Liver, EASL: European Association for the Study of the Liver; HBeAg+: initial e-Antigen positive population; HBeAg-: initial e-Antigen negative population; HBsAg: hepatitis B surface antigen

Table S2: Risk of Bias Assessment in Studies Exploring Viral Markers

Paper	D1	D2	D3	D4	D5	D6	D7	Overall
Honer Zu Siederdissen, C., et al 2016	Moderate	Low	Low	Low	Low	Low	Serious	Moderate
Hsu, Y.C., et al 2019	Moderate	Low	Low	Low	Moderate	Low	Moderate	Moderate
Carey, I., et al 2020	Low	Moderate	Low	Low	Moderate	Low	Moderate	Moderate
Fan, R., et al 2020	Moderate	Low	Low	Low	Low	Low	Moderate	Low
Fan, R., et al 2020B	Moderate	Low	Low	Low	Low	Low	Moderate	Low
Garcia-Lopez, M., et al 2020	Moderate	Low	Low	Low	Low	Low	Moderate	Low
Kaewdech, A., et al 2020	Moderate	Low	Low	Low	Low	Low	Serious	Moderate
Lai, C.L., et al 2020	Moderate	Low	Low	Low	Low	Low	Moderate	Low
Liu, Y., et al 2020	Moderate	Moderate	Low	Low	Moderate	Low	Moderate	Moderate
Papatheodoridi, M., et al 2020	Moderate	Low	Low	Low	Moderate	Low	Moderate	Moderate
Seto, W.K., et al 2020	Moderate	Low	Low	Low	Low	Low	Moderate	Low
Tseng, T.N., et al 2020*	Moderate	Low	Low	Low	Moderate	Low	Moderate	Moderate
Cheng, H.R., et al 2021	Moderate	Low	Low	Low	Low	Low	Moderate	Low
Huang, P.Y., et al 2021	Moderate	Low	Low	Low	Low	Low	Low	Low
Kuo, Y.H., et al 2021	Moderate	Low	Low	Low	Low	Low	Low	Low
Liao, G., et al 2021	Moderate	Low	Low	Low	Low	Low	Moderate	Low
Sonneveld, M.J., et al 2022A	Moderate	Low	Low	Low	Low	Low	Low	Low
Wubbolding, L.A., et al 2021	Moderate	Low	Low	Low	Low	Low	Serious	Moderate
Xia, M., et al 2021	Moderate	Low	Low	Low	Low	Low	Low	Low
Xie, Y., et al 2021	Moderate	Low	Low	Low	Low	Low	Low	Low
Chen, C.H., et al 2022	Moderate	Low	Low	Low	Low	Low	Moderate	Low
Kaewdech, A., et al 2022	Moderate	Low	Low	Low	Low	Low	Moderate	Low
Papatheodoridi, M., et al 2022	Moderate	Low	Low	Low	Low	Low	Moderate	Low
Sonneveld, M.J., et al 2022B	Moderate	Low	Low	Low	Low	Low	Low	Low

Bias Domains included in the Robins-I tool

D1: Bias due to confounding
D2: Bias in selection of participants into the study
D3: Bias in classification of interventions
D4: Bias due to deviations from intended interventions
D5: Bias due to missing data
D6: Bias in measurement of the outcome
D7: Bias in selection of the reported result

Table S3: Comparison of HBV RNA Platforms

Paper	HBV RNA Platform	Lower Limit of Detection
Carey, I., et al 2020	m2000 system (Abbott Molecular)	1.65 log U/mL
Fan, R., et al 2020	LightCycler 480 Instrument II system (Roche, Mannheim, Germany) with Taqman probe method	3 log U/mL
Fan, R., et al 2020	LightCycler 480 Instrument II system (Roche, Mannheim, Germany) with Taqman probe method	3 log U/mL
Garcia-Lopez, et al 202	TaqMan Fast Virus 1-Step Master Mix (Applied Biosystems, Thermo Fisher Scientific, Waltham, MA, USA)	6 copies per reaction
Kaewdech, A., et al 202	Droplet digital PCR (Bio-Rad, Hercules, CA, USA)	2 log copies/mL
Lai, C.L., et al 202	LightCycler 1.5 (Roche Applied Science, Mannheim, Germany)	800 copies/mL
Liu, Y., et al 202	AutoSAT system (Rendu Biotechnology)	100 copies/mL
Seto, W.K., et al 202	m2000 system (Abbott Molecular)	1.65 log U/mL
Xia, M., et al, 2021	LightCycler 480 Instrument II system (Roche, Mannheim, Germany) with Taqman probe method	3 log U/mL
Xie, Y., et al 202	ABI Prism 7500 Real-time PCR System (ABI, USA)	Not specified
Kaewdech, A., et al 202	Droplet digital PCR (Bio-Rad, Hercules, CA, USA)	2 log copies/mL
Papatheodoridi, M., et al 202	LightCycler 1.5 (Roche Applied Science, Mannheim, Germany)	10 copies per reaction or 1320 copies/mL