Uncovering Occult HBV Replication in People With HIV Using High-Sensitivity HBcrAg Assay

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BACKGROUND

- People with HIV (PWH) remain at risk for hepatitis B virus (HBV) co-infection and reactivation.
- Antiretroviral regimens without anti-HBV activity are increasingly used.
- Occult HBV infection may escape detection by conventional serologic markers, particularly in isolated anti-HBc cases.
- **High-sensitivity HB core-related antigen (iTACT-HBcrAg), an ultrasensitive immunoassay for HB-core-related proteins (PreC(p22cr), HBeAg, and HBc(p21))** may uncover residual viral activity in this population.

METHODS

- We performed a retrospective study of PWH attending our clinic between January 2023 and March 2024.
- Among 550 PWH screened for HBV serological markers.
- Seropositivity was defined as HBsAg > 0.05IU/mL, anti-HBs > 10mIU/mL, anti-HBc > 1.0 S/CO.
- A cutoff of iTACT-HBcrAg was 2.1 log IU/mL.
- IRB approval: IMSUT-IRB 2022-48-1128

CONCLUSIONS

- A subset of anti-HBc–positive PWH harbored detectable HBV viral protein activity despite negative HBsAg, with four cases of occult HBV infection identified by iTACT-HBcrAg.
- These findings underscore the potential risk of HBV reactivation in patients receiving antiretroviral therapy without HBV-active agents.
- iTACT-HBcrAg testing may provide important guidance for antiretroviral therapy selection and for long-term risk stratification and preventive strategies in this population.

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High-sensitivity HBcrAg uncovered occult HBV infection beyond conventional serologic markers in PWH.

These findings raise concern for potential HBV reactivation when ART without HBV-active agents is used.

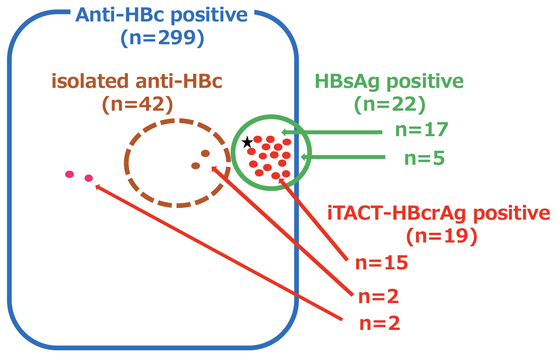
RESULTS

Table1：Baseline characteristic and Seroprevalence of hepatitis B markers

Baseline characteristic	All patients n=550	
Age (years) *	51	(44-58)
Male	524	(95.3%)
on ART	549	(99.8%)
Duration of ART (years) *#	13	(10-17)
HIV viral load <50 copies/mL	505	(91.8%)
CD4 count (/μl) *	592	(447-762)
CD8 count (/μl) *	701	(530-908)
CD4/CD8 ratio*	1.0	(0.62-1.14)
anti-HBc positive	299	(54.4%)
Isolated anti-HBc §	42	(7.6%)
HBs-Ag positive	22	(4.0%)
HBs-Ag and/or anti-HBc positive	304	(55.3%)
anti-HBs positive	325	(59.1%)

*Median(interquartile range), #n=517,
§negative for both HBsAg and anti-HBs

Figure：Distribution of iTACT-HBcrAg–positive cases among anti-HBc–positive PWH.



★ ant-HBc and HBsAg positive but negative for both iTACT-HBcrAg and HBV DNA

- **55.3%** had evidence of past or current HBV infection, comprising **54.4%** with anti-HBc and 4.0% with HBsAg.
- Among anti-HBc–positive individuals, 14.1% (42/299) had isolated anti-HBc (HBsAg−/anti-HBs−), representing **7.6%** (42/550) of the overall cohort.
- Of 286 anti-HBc–positive PWH, **6.6%** (19/286) tested positive for iTACT-HBcrAg.

Table2：Characteristics of iTACT-HBcrAg-positive 19 PWH

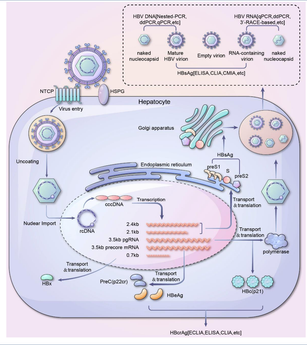
Patient No.	Age	iTACT HBcrAg (LogU/mL)	HBs-Ag (IU/mL)	Anti-HBs (mIU/mL)	Anti-HBc (S/CO)	HBV-DNA (LIU/mL)	HBV genotype	AST/ALT (U/L)	ART	CD4 count (/μL)
1	52	7.1	68856.01	0.62	6.7	2	A	85/126	TAF/FTC/BIC	512
2	54	5.2	956.62	0.3	2.2	ND	unknown	24/26	TAF/FTC DOR	608
3	38	5.0	1114.84	0.52	5.4	ND	A	28/40	TAF/FTC DOR	554
4	66	4.7	2262.69	0.14	5.3	ND	A	18/14	TAF/FTC, DTG	976
5	53	4.4	2697.06	0	5.9	ND	C	16/17	TAF/FTC/DRV/ cobi DTG	426
6	42	4.2	0.13	0.77	7.7	ND	A	17/10	TAF/FTC/BIC	1061
7	75	4	82.72	0.36	6.3	ND	A	17/13	TAF/FTC/BIC	560
8	57	4	0.02	1.06	6.8	ND	unknown	15/10	TAF/FTC/BIC	230
9	38	4	17772.94	0	7.7	ND	A	20/22	TAF/FTC/BIC	370
10	66	3.1	0	128.62	6.5	ND	A	22/15	TAF/FTC, DTG	394
11	65	3	173.15	0.81	4.6	ND	A	39/37	TAF/FTC/BIC	900
12	52	2.9	17507.08	0	7.4	ND	A	29/20	TAF/FTC/BIC	443
13	51	2.9	12.62	2.06	7.7	ND	A	33/65	TAF/FTC/BIC	448
14	44	2.7	1712.3	0.54	7.8	ND	A	20/34	TAF/FTC/BIC	898
15	57	2.7	2.03	1.49	2.39	ND	A	17/17	TAF/FTC/BIC	424
16	55	2.6	0	1.01	4.8	ND	C	15/20	TAF/FTC/BIC	1031
17	73	2.4	486.76	0.04	5.7	ND	C	21/31	3TC/DTG/ETV	331
18	54	2.2	0	44.5	6.5	ND	unknown	19/20	TAF/FTC/DTG	632
19	57	2.2	4.59	0.49	4.5	ND	A	21/20	TAF/FTC/BIC	742

- All 19 PWH were receiving two antiretroviral agents with anti-HBV activity.
- Among iTACT-HBcrAg–positive PWH, 94.4% (18/19) were HBV DNA negative, and 77.8%(15/19) were HBsAg positive.
- The two HBsAg-negative cases had an **isolated anti-HBc profile; one positive by high-sensitivity HBsAg** (#8: 0.016 IU/mL), whereas the other remained negative (#16: <0.005IU/mL).
- Notably, **two additional cases had undetectable high-sensitivity HBsAg but detectable anti-HBs** (#10: 128.62 mIU/mL; #18: 44.5 mIU/mL).
- One case was anti-HBc positive (6.7s/co) and HBsAg positive (36.37IU/mL) but negative for both iTACT-HBcrAg and HBV DNA.

REFERENCES

Detection technology and clinical application of serum viral products of HBV infection

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PLAIN LANGUAGE SUMMARY

A new, highly sensitive test detected hidden hepatitis B replication in some people with HIV who appeared negative on routine tests.
These findings may help doctors choose safer HIV treatments and better prevent hepatitis B reactivation.