

## Supporting information

**S1 Table.** Risk of hepatocellular carcinoma associated with different categories of increasing consecutive months with both undetectable HIV RNA and undetectable hepatitis B virus (HBV) DNA as well as consecutive months of undetectable (HBV) DNA alone among HIV/HBV-coinfected persons who received HBV-active antiretroviral therapy in the North American AIDS Cohort Collaboration on Research and Design (1995-2016; n=4,891; 78 incident hepatocellular carcinoma events identified).

Characteristic*	No. Exposed <sup>†</sup>	No. Events	Person-Time	Incidence Rate (95% CI), Events/1,000 Person-Years	Unadjusted HR (95% CI)	Adjusted HR <sup>‡,§</sup> (95% CI)
<b>Duration of Detectable HBV</b>	3,226	38	11,529	3.3 (2.3-4.5)	Reference	Reference
Undetectable HBV for <0.5 year	2,866	7	1,485	4.7 (1.9-9.7)	1.56 (0.69-3.53)	1.04 (0.40-2.72)
Undetectable HBV for 0.5-1 year	3,102	6	1,625	3.7 (1.4-8.0)	1.27 (0.53-3.05)	1.22 (0.50-2.97)
Undetectable HBV for 1-2 years	2,843	4	2,799	1.4 (0.4-3.7)	0.46 (0.16-1.29)	0.44 (0.15-1.27)
Undetectable HBV for 2-3 years	2,433	4	2,336	1.7 (0.5-4.4)	0.59 (0.21-1.68)	0.59 (0.21-1.71)
Undetectable HBV for 3-4 years	2,097	4	1,971	2.0 (0.6-5.2)	0.67 (0.24-1.91)	0.65 (0.22-1.87)
Undetectable HBV for ≥4 years	1,773	15	8,374	1.8 (1.0-3.0)	0.46 (0.25-0.84)	0.34 (0.17-0.68)
<b>Duration of Detectable HIV and HBV</b>	4,181	40	13,923	2.9 (2.1-3.9)	Reference	Reference
Undetectable HIV and HBV for <0.5 year	3,112	10	2,238	4.5 (2.1-8.2)	1.66 (0.83-3.34)	1.54 (0.76-3.11)
Undetectable HIV and HBV for 0.5-1 year	2,885	5	1,829	2.7 (0.9-6.4)	0.96 (0.37-2.44)	0.89 (0.35-2.29)
Undetectable HIV and HBV for 1-2 years	2,609	3	2,831	1.1 (0.2-3.1)	0.38 (0.12-1.22)	0.35 (0.11-1.15)
Undetectable HIV and HBV for 2-3 years	2,132	4	2,127	1.9 (0.5-4.8)	0.68 (0.24-1.93)	0.62 (0.22-1.77)
Undetectable HIV and HBV for 3-4 years	1,730	6	1,639	3.7 (1.3-8.0)	1.30 (0.54-3.11)	1.15 (0.47-2.79)
Undetectable HIV and HBV for ≥4 years	1,396	10	5,399	1.9 (0.9-3.4)	0.54 (0.27-1.11)	0.38 (0.17-0.85)

Abbreviations: CI=confidence interval; HBV=hepatitis B virus; HIV=human immunodeficiency virus; HR=hazard ratio

\* Detectable HIV=HIV RNA >500 copies/mL; Detectable HBV=HBV DNA identified on quantitative or qualitative assay; Undetectable HIV=HIV RNA ≤500 copies/mL; Undetectable HBV=no HBV DNA identified on quantitative or qualitative assay.

<sup>†</sup> Since HIV RNA and HBV DNA are time-updated variables, a given patient may be included within more than one category.

<sup>‡</sup> Models adjusted for age, sex, race/ethnicity, diabetes, time-updated HIV RNA, time-updated CD4+ cell percentage, heavy alcohol use, and year at start of follow-up.

<sup>§</sup> Test for trend for detectable HIV and HBV analysis: p=0.0167; test for trend for detectable HBV analysis: p=0.0014.

**S2 Table.** Factors associated with hepatocellular carcinoma among HIV/hepatitis B virus-coinfected persons in the North American AIDS Cohort Collaboration on Research and Design (1995-2016; n=8,354; 115 incident hepatocellular carcinoma events identified), based on multivariable Cox regression analysis accounting for death as a competing risk.

Characteristic	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)
<b>Age</b>		
<40 years	Reference	Reference
40-49 years	2.20 (1.38-3.52)	1.96 (1.22-3.14)
≥50 years	2.80 (1.68-4.67)	2.53 (1.50-4.27)
<b>Sex</b>		
Female	Reference	Reference
Male	2.61 (0.83-8.24)	1.92 (0.59-6.19)
<b>Race</b>		
Non-white	Reference	Reference
White	1.30 (0.90-1.88)	1.38 (0.93-2.04)
<b>Body Mass Index</b>		
Not obese (<30 kg/m <sup>2</sup> )	Reference	Reference
Obese (≥30 kg/m <sup>2</sup> )	0.99 (0.54-1.79)	1.00 (0.55-1.81)
<b>Diabetes mellitus<sup>†‡</sup></b>		
No	Reference	Reference
Yes	2.06 (1.10-3.85)	1.78 (0.95-3.34)
<b>Heavy alcohol use<sup>§</sup></b>		
No	Reference	Reference
Yes	1.62 (1.12-2.36)	1.53 (1.05-2.22)
<b>Chronic hepatitis C virus infection<sup>  </sup></b>		
No	Reference	Reference
Yes	1.78 (1.22-2.62)	1.60 (1.07-2.39)
<b>Current HIV RNA<sup>†</sup></b>		
≤500 copies/mL	Reference	Reference
>500 copies/mL	0.88 (0.56-1.39)	0.89 (0.55-1.44)
<b>Current CD4+ cell percentage</b>		
>28%	Reference	Reference
14-27.99%	1.47 (0.98-2.20)	1.46 (0.97-2.20)
<14%	0.97 (0.53-1.76)	1.02 (0.54-1.89)
<b>Year at start of follow-up</b>	0.96 (0.91-1.02)	0.95 (0.89-1.01)

Abbreviations: CI=confidence interval; HBV=hepatitis B virus; HIV=human immunodeficiency virus; HR=hazard ratio; RNA=ribonucleic acid

\* Hazard ratios adjusted for all other risk factors.

† Evaluated as a time-varying covariate.

‡ Diabetes mellitus was defined by: 1) hemoglobin A1c >6.5%, 2) prescription of anti-diabetic medication, or 3) record of a diabetes diagnosis plus the prescription of diabetes-related medication prior to start of follow-up.

§ History of heavy alcohol use defined as ever having reported while under observation in the NA-ACCORD: 1) inpatient or outpatient diagnosis of alcohol dependence/abuse, or 2) ≥3 drinks/day or ≥7 drinks/week for females; ≥4 drinks/day or ≥14 drinks/week for males on the self-reported Alcohol Use Disorders Identification Test-Consumption questionnaire.

|| Chronic hepatitis C virus infection was defined by detectable HCV RNA or available HCV genotype recorded at any time during observation.

**S3 Table.** Risk of hepatocellular carcinoma associated with time-updated hepatitis B virus (HBV) DNA level and time-updated detectable HIV and HBV status among HIV/HBV-coinfected persons who had quantitative and/or qualitative HBV DNA assessed in the North American AIDS Cohort Collaboration on Research and Design (1995-2016; n=5,316; 87 incident hepatocellular carcinoma events identified), based on multivariable Cox regression analysis accounting for death as a competing risk.

Characteristic	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)
<b>Time-Updated HBV DNA</b>		
Undetectable	Reference	Reference
Detectable	1.85 (1.21-2.84)	2.20 (1.40-3.44)
<b>Time-Updated Detectable HIV and HBV Status†</b>		
Undetectable HIV and HBV	Reference	Reference
Detectable HIV, undetectable HBV	0.29 (0.07-1.23)	0.27 (0.06-1.16)
Undetectable HIV, detectable HBV	1.54 (0.95-2.52)	1.75 (1.04-2.96)
Detectable HIV and HBV	1.89 (1.03-3.50)	2.16 (1.11-4.23)

Abbreviations: CI=confidence interval; HBV=hepatitis B virus; HIV=human immunodeficiency virus; HR=hazard ratio  
 \* Model evaluating time-updated HBV DNA adjusted for age, sex, race/ethnicity, diabetes, time-updated HIV RNA, time-updated CD4+ cell percentage, heavy alcohol use, and year at start of follow-up. Model evaluating time-updated detectable HIV and HBV status adjusted for adjusted for age, sex, race/ethnicity, diabetes, time-updated CD4+ cell percentage, heavy alcohol use, and year at start of follow-up.

† HIV detectable=HIV RNA >500 copies/mL; HBV detectable=HBV DNA identified on quantitative or qualitative assay; HIV suppressed=HIV RNA ≤500 copies/mL; HBV undetectable=no HBV DNA identified on quantitative or qualitative assay.

**S4 Table.** Risk of hepatocellular carcinoma associated with different categories of increasing consecutive months with undetectable (HBV) DNA and, separately, both undetectable HIV RNA and HBV DNA, among HIV/HBV-coinfected persons who had quantitative or qualitative HBV DNA assessed and received HBV-active antiretroviral therapy in the North American AIDS Cohort Collaboration on Research and Design (1995-2016; n=4,891; 78 incident hepatocellular carcinoma events identified), based on multivariable Cox regression analysis accounting for death as a competing risk.

Characteristic*	Unadjusted HR (95% CI)	Adjusted HR <sup>†</sup> (95% CI)
<b>Duration of Undetectable HBV</b>		
Detectable HBV	Reference	Reference
Undetectable HBV for <1 year	1.41 (0.74-2.71)	1.12 (0.54-2.32)
Undetectable HBV for ≥1 year	0.50 (0.30-0.82)	0.42 (0.24-0.74)
<b>Duration of Undetectable HBV</b>		
Detectable HBV	Reference	Reference
Undetectable HBV for <1 year	1.42 (0.74-2.73)	1.14 (0.55-2.35)
Undetectable HBV for 1-4 years	0.56 (0.29-1.06)	0.55 (0.28-1.06)
Undetectable HBV for ≥4 years	0.45 (0.25-0.84)	0.34 (0.16-0.68)
<b>Duration of Undetectable HIV and HBV</b>		
Detectable HIV and HBV	Reference	Reference
Undetectable HIV and HBV for <1 year	1.34 (0.74-2.44)	1.25 (0.67-2.31)
Undetectable HIV and HBV for ≥1 year	0.62 (0.37-1.05)	0.51 (0.29-0.90)
<b>Duration of Undetectable HIV and HBV</b>		
Detectable HIV and HBV	Reference	Reference
Undetectable HIV and HBV for <1 year	1.34 (0.74-2.44)	1.24 (0.67-2.31)
Undetectable HIV and HBV for 1-4 years	0.70 (0.38-1.31)	0.64 (0.34-1.21)
Undetectable HIV and HBV for ≥4 years	0.54 (0.26-1.11)	0.38 (0.18-0.81)

Abbreviations: CI=confidence interval; HBV=hepatitis B virus; HIV=human immunodeficiency virus; HR=hazard ratio  
 \* Detectable HIV=HIV RNA >500 copies/mL; Detectable HBV=HBV DNA identified on quantitative or qualitative assay; Undetectable HIV=HIV RNA ≤500 copies/mL; Undetectable HBV=no HBV DNA identified on quantitative or qualitative assay.

<sup>†</sup> Models adjusted for age, sex, race/ethnicity, diabetes, time-updated HIV RNA, time-updated CD4+ cell percentage, heavy alcohol use, and year at start of follow-up.

**S5 Table.** Factors associated with hepatocellular carcinoma among HIV/hepatitis B virus-coinfected persons in the North American AIDS Cohort Collaboration on Research and Design (1995-2016), stratified by platelet count (<150,000/ $\mu$ L;  $\geq$ 150,000/ $\mu$ L) at the start of follow-up.

Characteristic	Platelet Count <150,000/ $\mu$ L (n=1,584; 51 incident HCC events)			Platelet Count $\geq$ 150,000/ $\mu$ L (n=6,285; 61 incident HCC events)		
	Person-Time	No. Events	Unadjusted HR (95% CI)	Person-Time	No. Events	Unadjusted HR (95% CI)
<b>Age</b>						
<40 years	3,621	10	Reference	20,010	14	Reference
40-49 years	4,693	27	2.06 (1.00-4.27)	20,137	28	1.94 (1.02-3.70)
$\geq$ 50 years	2,327	14	2.24 (0.99-5.04)	10,198	19	2.80 (1.40-5.60)
<b>Sex</b>						
Female	568	1	Reference	3,379	2	Reference
Male	10,072	50	2.74 (0.38-19.82)	46,967	59	2.08 (0.51-8.54)
<b>Race</b>						
Non-white	4,872	15	Reference	26,795	35	Reference
White	5,768	36	1.99 (1.09-3.64)	23,551	26	0.82 (0.49-1.36)
<b>Body Mass Index</b>						
Not obese (<30 kg/m <sup>2</sup> )	8,952	41	Reference	42,445	52	Reference
Obese ( $\geq$ 30 kg/m <sup>2</sup> )	1,061	7	1.38 (0.62-3.08)	5,751	5	0.78 (0.31-1.95)
<b>Diabetes mellitus<sup>††</sup></b>						
No	10,096	45	Reference	47,741	56	Reference
Yes	543	6	2.60 (1.10-6.11)	2,605	5	1.69 (0.68-4.21)
<b>Heavy alcohol use<sup>§</sup></b>						
No	6,166	25	Reference	27,696	25	Reference
Yes	4,166	26	1.51 (0.87-2.62)	21,489	35	1.70 (1.01-2.84)
<b>Hepatitis C virus coinfection<sup>  </sup></b>						
No	7,571	36	Reference	39,379	36	Reference
Yes	3,069	15	1.01 (0.55-1.85)	10,967	25	2.44 (1.47-4.07)
<b>Current HIV RNA<sup>†</sup></b>						
$\leq$ 500 copies/mL	7,413	37	Reference	35,270	47	Reference
>500 copies/mL	3,227	14	0.98 (0.52-1.86)	15,076	14	0.92 (0.50-1.71)
<b>Current CD4+ cell percentage<sup>†</sup></b>						
>28%	3,508	17	Reference	20,664	22	Reference
14-27.99%	4,601	28	1.29 (0.70-2.36)	20,933	29	1.45 (0.83-2.53)
<14%	2,531	6	0.54 (0.21-1.38)	8,749	10	1.32 (0.62-2.82)
<b>Year at start of follow-up</b>	-	-	0.97 (0.90-1.05)	-	-	0.95 (0.87-1.04)

Abbreviations: CI=confidence interval; HBV=hepatitis B virus; HCC=hepatocellular carcinoma; HIV=human immunodeficiency virus; HR=hazard ratio

<sup>\*</sup> There were too few events to permit a fully-adjusted model comparable to that in **Table 2** in the main manuscript.

<sup>†</sup> Evaluated as a time-varying covariate.

<sup>‡</sup> Diabetes mellitus was defined by: 1) hemoglobin A1c >6.5%, 2) prescription of anti-diabetic medication, or 3) record of a diabetes diagnosis plus the prescription of diabetes-related medication prior to start of follow-up.

<sup>§</sup> History of heavy alcohol use defined as ever having reported while under observation in the NA-ACCORD: 1) inpatient or outpatient diagnosis of alcohol dependence/abuse, or 2)  $\geq$ 3 drinks/day or  $\geq$ 7 drinks/week for females;  $\geq$ 4 drinks/day or  $\geq$ 14 drinks/week for males on the self-reported Alcohol Use Disorders Identification Test-Consumption questionnaire.

<sup>||</sup> Chronic hepatitis C virus infection was defined by detectable HCV RNA or available HCV genotype recorded at any time during observation.

**S6 Table.** Risk of hepatocellular carcinoma associated with time-updated hepatitis B virus (HBV) DNA level and time-updated detectable HIV and HBV status among HIV/hepatitis B virus-coinfected persons who had quantitative or qualitative HBV DNA assessed in the North American AIDS Cohort Collaboration on Research and Design (1995-2016), stratified by platelet count (<150,000/ $\mu$ L;  $\geq$ 150,000/ $\mu$ L) at the start of follow-up.

Characteristic	Platelet Count <150,000/ $\mu$ L (n=1,075; 42 incident HCC events)			Platelet Count $\geq$ 150,000/ $\mu$ L (n=3,954; 43 incident HCC events)		
	Person-Time	No. Events	Unadjusted HR (95% CI)	Person-Time	No. Events	Unadjusted HR (95% CI)
<b>Time-Updated HBV DNA</b>						
Undetectable	3,417	24	Reference	18,075	19	Reference
Detectable	2,821	18	0.91 (0.49-1.70)	9,295	24	2.90 (1.58-5.32)
<b>Time-Updated Detectable HIV and HBV Status<sup>†</sup></b>						
Undetectable HIV and HBV	2,981	23	Reference	15,136	18	Reference
Detectable HIV, undetectable HBV	436	1	0.31 (0.04-2.30)	6,086	17	0.39 (0.05-2.94)
Undetectable HIV, detectable HBV	1,906	9	0.61 (0.28-1.32)	2,939	1	2.75 (1.42-5.36)
Detectable HIV and HBV	914	9	1.34 (0.61-2.97)	3,208	7	2.48 (1.01-6.07)

Abbreviations: CI=confidence interval; HBV=hepatitis B virus; HIV=human immunodeficiency virus; HR=hazard ratio

\* There were too few events to permit a fully-adjusted model comparable to that in **Table 4** in the manuscript.

<sup>†</sup> Detectable HIV=HIV RNA >500 copies/mL; Detectable HBV=HBV DNA identified on quantitative or qualitative assay; Undetectable HIV=HIV RNA  $\leq$ 500 copies/mL; Undetectable HBV=no HBV DNA identified on quantitative or qualitative assay.

**S7 Table.** Risk of hepatocellular carcinoma associated with different categories of increasing consecutive months with undetectable (HBV) DNA and, separately, both undetectable HIV RNA and HBV DNA, among HIV/HBV-coinfected persons who had quantitative or qualitative HBV DNA assessed and received HBV-active antiretroviral therapy in the North American AIDS Cohort Collaboration on Research and Design (1995-2016), stratified by platelet count (<150,000/ $\mu$ L;  $\geq$ 150,000/ $\mu$ L) at the start of follow-up.

Characteristic*	Platelet Count <150,000/ $\mu$ L (n=984; 38 incident HCC events)			Platelet Count $\geq$ 150,000/ $\mu$ L (n=3,640; 38 incident HCC events)		
	Person-Time	No. Events	Unadjusted HR <sup>†</sup> (95% CI)	Person-Time	No. Events	Unadjusted HR <sup>†</sup> (95% CI)
<b>Duration of Undetectable HBV</b>						
Detectable HBV	2,519	15	Reference	8,280	22	Reference
Undetectable HBV for <1 year	570	9	2.68 (1.16-6.18)	2,368	4	0.85 (0.29-2.51)
Undetectable HBV for $\geq$ 1 year	2,273	14	1.06 (0.51-2.24)	12,527	12	0.32 (0.16-0.64)
<b>Duration of Undetectable HBV</b>						
Detectable HBV	2,519	15	Reference	8,280	22	Reference
Undetectable HBV for <1 year	570	9	2.66 (1.15-6.15)	2,368	4	0.85 (0.29-2.52)
Undetectable HBV for 1-4 years	1,156	6	0.93 (0.36-2.44)	5,597	5	0.41 (0.15-1.09)
Undetectable HBV for $\geq$ 4 years	1,117	8	1.20 (0.48-2.99)	6,930	7	0.27 (0.11-0.65)
<b>Duration of Undetectable HIV and HBV</b>						
Detectable HIV and HBV	2,836	16	Reference	10,274	23	Reference
Undetectable HIV and HBV for <1 year	712	10	2.43 (1.09-5.41)	3,152	5	0.84 (0.32-2.22)
Undetectable HIV and HBV for $\geq$ 1 year	1,778	12	1.27 (0.59-2.76)	9,657	10	0.39 (0.18-0.82)
<b>Duration of Undetectable HIV and HBV</b>						
Detectable HIV and HBV	2,836	16	Reference	3,078	23	Reference
Undetectable HIV and HBV for <1 year	712	10	2.42 (1.09-5.39)	2,404	5	0.84 (0.32-2.22)
Undetectable HIV and HBV for 1-4 years	1,065	6	1.10 (0.42-2.84)	2,015	6	0.53 (0.21-1.30)
Undetectable HIV and HBV for $\geq$ 4 years	713	6	1.55 (0.57-4.19)	1,113	4	0.27 (0.09-0.80)

Abbreviations: CI=confidence interval; HBV=hepatitis B virus; HIV=human immunodeficiency virus; HR=hazard ratio

\* Detectable HIV=HIV RNA >500 copies/mL; Detectable HBV=HBV DNA identified on quantitative or qualitative assay; Undetectable HIV=HIV RNA  $\leq$ 500 copies/mL; Undetectable HBV=no HBV DNA identified on quantitative or qualitative assay.

<sup>†</sup> There were too few events to permit a fully-adjusted model comparable to that in **Table 5** in the manuscript.

**S8 Table.** Exploratory analysis examining risk of hepatocellular carcinoma (HCC) associated with platelet count <150,000/ $\mu$ L, after adjustment for time-updated detectable hepatitis B virus (HBV), time-updated detectable HIV, time-updated CD4+ cell percentage, and specified traditional HCC risk factors among HIV/HBV-coinfected persons who had quantitative and/or qualitative HBV DNA assessed in the North American AIDS Cohort Collaboration on Research and Design (1995-2016; n=5,029; 85 incident hepatocellular carcinoma events identified).

Characteristic	No. Exposed	No. Events	Person-Time	Incidence Rate (95% CI), Events/1,000 Person-Years	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)
<b>Platelet Count (<math>\mu</math>L)</b>						
≥150,000	3,954	43	27,369	1.6 (1.1-2.1)	Reference	Reference
<150,000	1,075	42	6,237	6.7 (4.9-9.1)	4.51 (2.94-6.91)	4.05 (2.62-6.26)
<b>Time-Updated HBV DNA</b>						
Undetectable	3,444	43	21,492	2.0 (1.4-2.7)	Reference	Reference
Detectable	3,171	42	12,115	3.5 (2.5-4.7)	1.89 (1.23-2.91)	1.89 (1.20-2.98)

Abbreviations: CI=confidence interval; HBV=hepatitis B virus; HCC=hepatocellular carcinoma; HIV=human immunodeficiency virus; HR=hazard ratio

\* Model additionally adjusted for age, sex, race/ethnicity, diabetes, time-updated HIV RNA, time-updated CD4+ cell percentage, heavy alcohol use, and year at start of follow-up.