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HIV, hepatitis B virus, and hepatitis C virus co-infection in patients in the China National Free Antiretroviral Treatment Program, 2010–12: a retrospective observational cohort study

Fujie Zhang, Hao Zhu, Yasong Wu, Zhihui Dou, Yao Zhang, Nora Kleinman, Marc Bulterys, Zunyou Wu, Ye Ma, Decai Zhao, Xia Liu, Hua Fang, Jing Liu, Wei-Ping Cai, and Hong Shang
National Center for AIDS/STD Control and Prevention, China Center for Disease Control and Prevention, Beijing, China (Prof F Zhang MD, Y Wu MD, Z Dou MSPH, Y Zhang MD, Z Wu PhD, Prof Y Ma PhD, D Zhao MSPH, X Liu PhD, H Fang MSPH); First Affiliated Hospital of China Medical University, Liaoning, China (F Zhang, J Liu MD, Prof H Shang MD); Global AIDS Program, China Office, US Centers for Disease Control and Prevention, Beijing, China (H Zhu PhD, N Kleinman MSPH, M Bulterys MD); Association of Schools and Programs of Public Health, Washington, DC, USA (N Kleinman); Department of Infectious Diseases, Guang Zhou Eighth People's Hospital, Guangdong, China (W-P Cai MD); and Department of Defense HIV/AIDS Prevention Program, Naval Health Research Center, San Diego, CA, USA (M Bulterys)

Summary

Background—Hepatitis-related liver diseases are a leading cause of mortality and morbidity among people with HIV/AIDS taking combination antiretroviral therapy. We assessed the effect of hepatitis B virus (HBV) and hepatitis C virus (HCV) co-infection on HIV outcomes in patients in China.

Methods—We did a nationwide retrospective observational cohort study with data from the China National Free Antiretroviral Treatment Program from 2010–11. Patients older than 18 years starting standard antiretroviral therapy for HIV who had tested positive for HBV and HCV were followed up to Dec 31, 2012. We used Kaplan-Meier analysis and Cox proportional hazard models to evaluate survival, and logistic regression models to estimate virological failure, immunological response, and retention in care.

Findings—33 861 patients with HIV met eligibility criteria. 2958 (8.7%) participants had HBV co-infection, 6149 (18.2%) had HCV co-infection, and 1114 (3.3%) had triple infection. All-cause mortality was higher in participants with triple infection (adjusted hazard ratio 1.90, 95% CI 1.53–2.37) and HCV co-infection (1.46, 1.25–1.70) than in those with HIV only, but not in those with

Correspondence to: Dr Hong Shang, Key Laboratory of AIDS Immunology of the Ministry of Health, Department of Laboratory Medicine, First Affiliated Hospital of China Medical University, No 155, Nanjing North Street, Heping District, Shenyang, 110001, China, hongshang100@hotmail.com.

Contributors

HS, FZ, HZ, and MB designed the study. DZ and HF collected the data. ZD and HZ analysed the data. YW, YZ, YM, XL, and JL interpreted the data. MB, W-PC, and ZW suggested additional analyses. ZD and HZ designed the figures. HZ and NK drafted the report. All authors reviewed, revised, and approved the final report.

Declaration of interests

We declare no competing interests.

HBV co-infection (1.06, 0.89–1.26). People with triple infection were also more likely to have virological failure (adjusted odds ratio [OR] 1.26, 95% CI 1.02–1.56) than were those with HIV only, whereas the difference was not significant for those with HBV co-infection (0.93, 0.80–1.10) or HCV co-infection (1.10, 0.97–1.26). No co-infection was significantly associated with a difference in CD4 cell count after 1 year of treatment. Loss to follow-up was more common among participants with triple infection (OR 1.37, 95% CI 1.16–1.62) and HCV co-infection (1.30, 1.17–1.45), but not HBV co-infection (0.93, 0.82–1.05), than among those with HIV only.

Interpretation—Screening for viral hepatitis is important in individuals diagnosed as HIV positive. Effective management for viral hepatitis should be integrated into HIV treatment programmes. Long-term data are needed about the effect of hepatitis co-infection on HIV disease progression.

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Introduction

HIV, hepatitis B virus (HBV), and hepatitis C virus (HCV) contribute substantially to the global burden of disease.^{1,2} Worldwide, an estimated 31.4–35.9 million people have HIV/AIDS, 350–400 million people have HBV, and 150–170 million have HCV.^{3–5} These viruses share routes of transmission and many people with HIV are co-infected with HBV and HCV, especially in some populations such as injection drug users and men who have sex with men.^{6–8} The prevalence of HBV co-infection ranges from 5% to 20% and HCV co-infection ranges from 5% to 15% in resource-limited regions.³ In New York City, the prevalence of HIV and HBV co-infection is 4.5%, that of HIV and HCV co-infection is 25.0%, and that of triple infection (HIV, HBV, and HCV) is 1.6%.⁹ The transmission routes and epidemiology of HBV and HCV in people with HIV differ between low-income and high-income countries.^{10,11} In low-income countries, most HBV infections occur in infancy or childhood through perinatal transmission or close household contact, and the main route of transmission for HCV is unsafe injection.^{1,12} In high-income countries, HBV is commonly transmitted through sexual contact and HCV through injection drug use and sex between men who have sex with men.^{10,12}

The introduction of combination antiretroviral therapy has greatly increased survival and decreased morbidity of people with HIV.^{13,14} As the life expectancy of people with HIV increases, chronic hepatitis-related liver diseases have become a growing concern.^{15,16} Additionally, hepatitis co-infection can complicate clinical management of HIV and increase hepatotoxicity.^{17,18}

HIV can accelerate hepatitis-related liver diseases.^{15,19} By contrast, the effect of HBV or HCV on HIV clinical progression, immunological response, and virological response has not been well established.^{20–22} Some researchers report that HIV and HBV co-infection increases the risk of virological failure and death²³ and that HIV and HCV co-infection decreases survival.²⁴ However, others found no effect of HBV or HCV on virological or immunological responses to combination antiretroviral therapy or mortality.²⁵ Moreover, very few data exist for the effect of triple viral co-infection on outcomes.

We assessed the effect of HBV and HCV co-infection on HIV clinical progression, virological and immunological responses, and retention in care in people with HIV receiving combination antiretroviral therapy in China.

Methods

Study design and participants

We did a nationwide clinical observational cohort study with data from the National Free Antiretroviral Treatment Program database, established and managed by the National Center for AIDS/STD Control and Prevention, China Center for Disease Control and Prevention (China CDC). The organisation, management, and workings of the database have been previously described.^{26,27} In brief, local health workers complete standardised reporting forms at baseline (initiation of antiretroviral therapy) and follow-up (0.5, 1, 2, and 3 months after initiation antiretroviral therapy, and every 3 months thereafter). Forms are entered into a web-based electronic data collection system and sent to the national office for data-cleaning and analysis.²⁸

We included participants if they were older than 18 years, treatment naive, started a standard treatment regimen between Jan 1, 2010, and Dec 31, 2011, and had HBV surface antigen and HCV antibody results recorded in the database. We included follow-up data up to Dec 31, 2012.

Since 2002, people with HIV in China with a CD4 count of 200 cells per μL or less, total lymphocyte count of less than 1200 cells per μL , or WHO disease stage 3 or 4 have been eligible for free combination antiretroviral therapy. In 2008, the CD4 count threshold for treatment was increased to 350 cells per μL .²⁹ Between 2003 and 2005, in agreement with WHO recommendations, the first-line HIV treatment regimen recommended in China was zidovudine or stavudine plus didanosine and nevirapine or efavirenz.²⁹ After 2005, these regimens were gradually replaced with zidovudine or stavudine plus lamivudine and nevirapine. Since 2010, stavudine has been phased out and tenofovir has been introduced in the first-line regimen, as recommended by WHO.³⁰

This study was approved by the Institutional Review Boards of the National Center for AIDS/STD Control and Prevention, China CDC in Beijing, and the Center for Global Health at the US CDC in Atlanta, GA, USA.

Procedures

We assessed four outcomes: survival, HIV virological response, HIV immunological response, and retention in treatment. We calculated survival as time from treatment initiation to death (all-cause and non-injury) or censoring. Patients were censored at dropout, loss to follow-up, or on Dec 31, 2012, whichever came first. We defined HIV virological suppression as plasma HIV RNA viral load less than 400 copies per mL after 6–18 months of combination antiretroviral therapy. We considered viral load of 400 copies per mL or more after 6–18 months of combination antiretroviral therapy as virological failure.³¹ We also assessed virological failure in three subgroups (400–1000 copies per mL, 1001–9999 copies per mL, and $\geq 10\,000$ copies per mL). We defined HIV immunological response as a

CD4 count increase of more than 30% compared with baseline after 9–15 months of combination antiretroviral therapy. We categorised retention status as retention, death, treatment withdrawal, or loss to follow-up (>90 days since a missed schedule visit).

We compared these four outcomes in four co-infection status groups: HIV mono-infection (HBV negative, HCV negative), HIV and HBV co-infection (HBV positive, HCV negative), HIV and HCV co-infection (HBV negative, HCV positive), and triple infection (HBV positive, HCV positive). We analysed covariates including sex, age (18–24, 25–29, 30–34, 35–39, 40–44, 45–54, and ≥55 years), self-reported mode of HIV transmission (blood transfusion or former plasma donor, injection drug use, sex with men who have sex with men, heterosexual sex), baseline CD4 count (<50, 50–199, 200–349, and ≥350 cells per μL), baseline alanine aminotransferase concentration (<40, 40–79, and ≥80 U/L), and baseline total bilirubin concentration (<17.1, 17.1–34.2, and ≥34.2 $\mu\text{mol/L}$).

HIV infection status was based on positive test results from two peripheral blood samples by HIV ELISA and confirmed by western blot. All HIV testing sites were certified by the National AIDS Reference Laboratory at China CDC. HBV chronic infection was defined by the presence in serum samples of HBsAg according to ELISA. We assessed serum HCV antibody positivity by second-generation or third-generation ELISA techniques; no information for HCV RNA testing was collected in the database.

Statistical analysis

We assessed characteristics by co-infection status with χ^2 tests (for categorical data) and non-parametric Wilcoxon tests (for continuous data). We assessed all-cause mortality and non-injury-related mortality by co-infection status with Kaplan-Meier analysis. We used log-rank tests to assess significance. We used Cox proportional hazard models to calculate unadjusted and adjusted hazard ratios (HRs) and 95% CIs. We tested deviations from the proportional hazard assumption by log-log survival plots. Because of the relation between HCV co-infection and injection drug use, for each multivariable analysis, we adjusted or stratified by transmission route (injection drug use or sexual contact).

We used logistic regression to estimate unadjusted and adjusted odds ratios (ORs) and 95% CIs for virological failure, immunological response, and treatment retention. As a sensitivity analysis for virological failure, we used two viral load cutoffs (>1000 and ≥10 000 copies per mL). We selected covariates a priori for inclusion in multivariable models on the basis of biological importance.^{27,31} We deemed a p value less than 0.05 as statistically significant for all analyses. We did the analyses with SAS (version 9.2).

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

70 694 people with HIV started combination antiretroviral therapy between 2010 and 2011, 36 833 of whom we excluded either because they lacked HBV or HCV testing results (n=35 855), or because they had not started a standard initial treatment regimen (n=978). 33 861 patients met eligibility criteria. 2958 (8.7%) participants had HBV co-infection, 6149 (18.2%) had HCV co-infection, and 1114 (3.3%) had triple infection. Two-thirds of participants were men with a median age of 37 years (table 1). About two-thirds of participants were infected through heterosexual transmission and almost half received antiretroviral treatment at a county or lower level hospital. Median CD4 count at treatment initiation was 195 cells per μL and most patients received zidovudine, lamivudine, and nevirapine or efavirenz as the initial regimen (table 1). Patients with HCV or triple infection, compared with those with HBV or HIV mono-infection, were more likely to be male ($p<0.001$), to have been infected by injection drug use ($p<0.001$), and to have initiated antiretroviral treatment at a county or lower level hospital ($p<0.001$). Median CD4 cell counts at baseline were higher in patients with triple infection and HCV infection than in those with HBV or HIV mono-infection (table 1).

2054 participants died from any cause during 556 400 person-months of follow-up. Median follow-up was 15 months (IQR 12–23). Median follow-up for participants with HCV (14 months) was slightly lower than that in the other three co-infection groups (15 months). The cumulative probability of all-cause death was 3.4% at 6 months, 5.0% at 12 months, and 7.6% at 24 months. In univariable analyses, compared with mono-infection, people with triple infection had the highest risk of death, followed by those with HCV co-infection, and HBV co-infection (table 2, figure 1A). A multivariable analysis adjusting for all covariates (table 2, appendix) showed that patients with HIV, HBV, and HCV were more likely to die than were those with HIV only ($p<0.0001$), as were those with HIV and HCV ($p<0.0001$). Participants with HIV and HBV did not have a significantly higher risk of death than those with HIV only ($p=0.51$; table 2). When stratified by transmission route, we found much the same associations, although the association of HCV co-infection with all-cause death was not significant for patients who had contracted HIV through injection drug use (table 2).

After excluding 166 participants who died of injuries, 33 695 remained in the analysis of non-injury death. The cumulative probability of non-injury death at each point was similar but lower than all-cause death (figure 1B). The associations between co-infection and non-injury death in univariable and multivariable analyses were consistent with the analyses of all-cause death (table 2).

23 991 participants had viral load test results. Viral suppression was rarest among people with triple infection (492 of 660; 74.5%), and more common among people with HCV and HIV (3023 of 3926; 77.0%), HIV and HBV (1873 of 2122; 88.3%), and HIV only (15 223 of 17 283; 88.1%; figure 2A). 12.9% of people with triple infection had a viral load of 10 000 copies per mL or more, compared with 11.9% of those with HCV–HIV co-infection, and 5.4% with HBV–HIV co-infection. In multivariable analysis, people with triple

See Online for appendix

infection were more likely to have virological failure than were those with mono-infection (figure 3). Patients co-infected with HCV were not significantly more likely to have virological failure. Virological failure occurred at much the same rate in participants co-infected with HIV and HBV, and those with HIV only (figure 3). Sensitivity analyses with different cutoffs for virological failure showed much the same results (figure 3).

25 303 patients had CD4 cell count test results. An immunological response occurred in 427 (59.8%) of 714 patients with triple infection, 2478 (60.1%) of 4125 with HIV and HCV, 1652 (74.1%) of 2230 with HIV and HBV, and 13 400 (73.5%) of 18 234 with HIV only (figure 2B). Change in CD4 cell count did not differ significantly between hepatitis co-infection groups and patients with HIV only (figure 3).

People with triple infection were most likely to be lost to follow-up, followed by those with HCV co-infection, those with HBV co-infection, and those with HIV only (figure 2C). In adjusted logistic regression analysis, non-retention in treatment was more likely in people with triple infection and HCV co-infection than in those with HIV infection only (figure 3). No significant difference occurred between those with HBV and HIV, and those with HIV only (figure 3).

Discussion

In this cohort of people being treated for HIV in China, 8.7% had HBV co-infection, 18.2% had HCV co-infection, and 3.3% had triple infection. Those with triple infection and HCV co-infection had a higher risk of death and not being retained in treatment. Triple infection also increased the risk of virological failure. Co-infection with HCV did not affect virological or immunological responses. Co-infection with HBV did not significantly affect any outcomes.

The prevalence of HBV co-infection in this study is lower than previously reported in Asia (14.6–21.7%),^{23,32} but higher than reported in the USA (4.5%).⁹ This difference is partly because of a greater proportion of men who have sex with men in previous studies. By contrast, the proportion of HCV co-infection in our study is higher than that previously reported in the Asia–Pacific region (7.2–10.4%).^{25,33} The predominant mode of HIV transmission in participants with HBV was heterosexual sex, which accords with other studies in Asia,^{32,33} but it was less common than reported in the USA and Europe.^{9,34} The primary mode of transmission of HIV among patients with HCV co-infection and triple infection was injection drug use, which occurred in much the same proportions as reported in the USA, Canada, and Europe.^{35,36} Patients infected from blood donation or transfusion were the largest known HIV-infected population in the early to mid-1990s in China.³⁷ However, few patients in our analysis were infected through this route, showing the benefits of blood donation screening policies. The prevalence of hepatitis co-infection varied by population characteristics in our study, and previous studies have reported variation by geographic location within China.²⁵

Our findings support results from most previous studies, showing that people with HIV and HCV have shorter survival even after starting antiretroviral treatment.^{22,38,39} By contrast,

one report showed no significant effect of HCV, which might be because of a smaller number of deaths than in our study.²⁵ Our findings also accord with previous studies showing no difference in survival between people with HIV and HBV, and those with HIV only,^{25,33} which could be related to the inclusion of lamivudine in the initial HIV treatment regimen.⁴⁰

People with triple infection had significantly worse virological responses than those with HIV only, a finding which has not previously been well documented. We recorded no other differences in virological or immunological responses, which is consistent with most previous studies.^{19,20,24,25,32,38} One study suggested that HBV infection could increase HIV virological failure,²³ but it was done in a single hospital with a high proportion of men who have sex with men so might not be generalisable.

Participants with triple infection or with HIV–HCV co-infection were less likely to be retained in treatment than were other participants. This finding is a concern, as maintenance of treatment and care is crucial to improve individual and public health outcomes.⁴¹ Low retention in these groups might, in part, be the result of them having a high proportion of injection drug users, who have a higher risk of leaving care and of death than other patients in China.^{41,42} However, other factors might also be involved. Additional research is needed to develop interventions aimed at increasing retention.

Our results should be interpreted within the study's limitations. First, HBV infection was diagnosed by HBsAg testing, which only measures presence or absence of antigen. We did not measure biomarkers that represent HBV activity status, and thus we were unable to identify acute HBV infection or HBV stage. This shortcoming might mean some individuals with acute infection were classified as having chronic disease, leading to overestimation of chronic HBV infection. However, this bias is somewhat balanced by missing the diagnosis of occult HBV infection (undetectable HBsAg in serum with the presence of HBV DNA), with proportions of occult HBV infection ranging from 3% to 11% in people with HIV.^{43,44} Second, HCV diagnosis was based on antibodies, not RNA. With the high prevalence of interleukin 28B genotype CC in Asia,⁴⁵ patients who might have cleared the infections were included in the HCV group, overestimating the prevalence of HCV infection.²⁰ Third, because of the little information for cause of death, we could not differentiate between non-AIDS-related and AIDS-related deaths. Hepatitis-related liver-disease deaths are common in people with HIV, therefore we might have overestimated the effect of hepatitis on HIV progression. However, we excluded patients with injury-related deaths, partly removing the effect of non-AIDS deaths. Fourth, we could not control for other factors, such as socioeconomic status, tobacco and alcohol use, and time since diagnosis, because these data were not collected in the database. Fifth, injection drug use might be under-reported, leading to confounding related to misclassification of transmission mode. Finally, ascertainment of death was not linked with a centralised death registry, thus mortality might be underestimated.⁴⁶

To the best of our knowledge, this is the first large, national cohort study to comprehensively assess survival, virological and immunological responses, and retention in care of people with HIV co-infected with HBV or HCV, or both (panel). Our findings emphasise the

importance of screening for viral hepatitis when individuals are identified as HIV positive. Moreover, effective management for viral hepatitis should be integrated into HIV treatment programmes, including effective treatment for triple infection and co-infection with HCV or HBV, and HBV vaccination for HBV-negative people with HIV to reduce HIV-related morbidity and mortality in regions in China where hepatitis is endemic. Long-term data are needed about the effect of hepatitis co-infection on HIV disease progression.

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Panel: Research in context**Systematic review**

We searched Medline with the terms “HIV”, “HBV”, “HCV”, and “co-infection”. We found several studies that show that HIV can accelerate hepatitis-related liver diseases.^{15,19} By contrast, the effect of infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) on HIV clinical progression, immunological response, and viral response has not been well established.^{20–22} Some studies have found no effect of hepatitis virus infection on viral and immunological response to combination antiretroviral therapy or mortality.²⁵ However, others have shown that HIV-HBV co-infection increases the risk of virological failure and death,²³ although our findings in the present study do not support this. Our study results support previous findings that HIV and hepatitis C virus co-infection decreases survival.²⁴ Very few data exist for the effect of triple viral infection. Our study suggests worse outcomes for those with triple infection compared with those with HIV alone.

Interpretation

These viruses share routes of transmission and many people with HIV are co-infected with HBV and HCV in China, particularly in injection drug users, sex workers, and men who have sex with men. Of an estimated 700 000 people with HIV in China about 10% also have HBV.⁴⁷ A systematic review of methadone maintenance treatment clinics in China showed 4-6% of attendees had HCV–HIV co-infection.⁴⁸ Our findings emphasise the importance of screening for viral hepatitis when individuals are diagnosed with HIV. Moreover, effective management of viral hepatitis should be integrated into HIV treatment programmes.

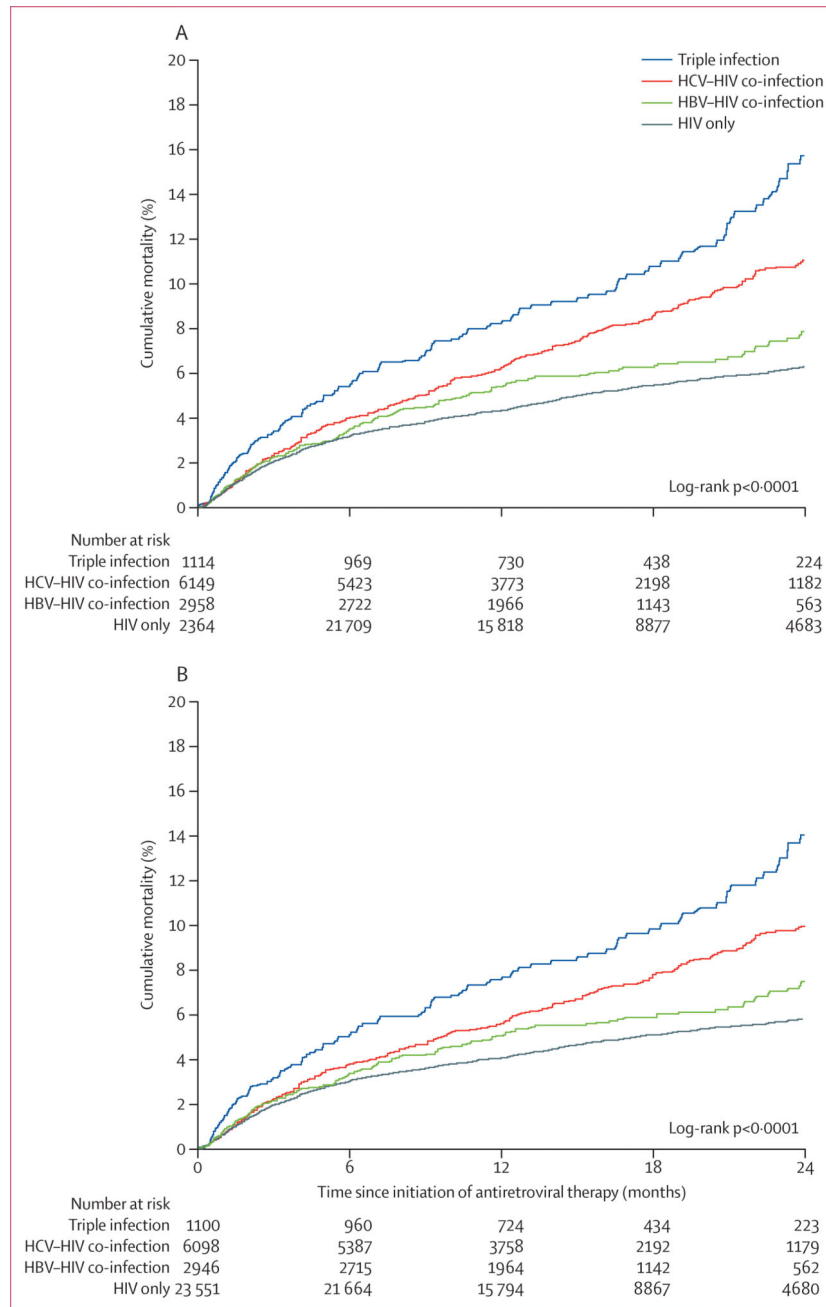


Figure 1. Cumulative probability of death, by hepatitis virus infection status
 (A) All-cause mortality and (B) non-injury mortality. HBV=hepatitis B virus.
 HCV=hepatitis C virus.

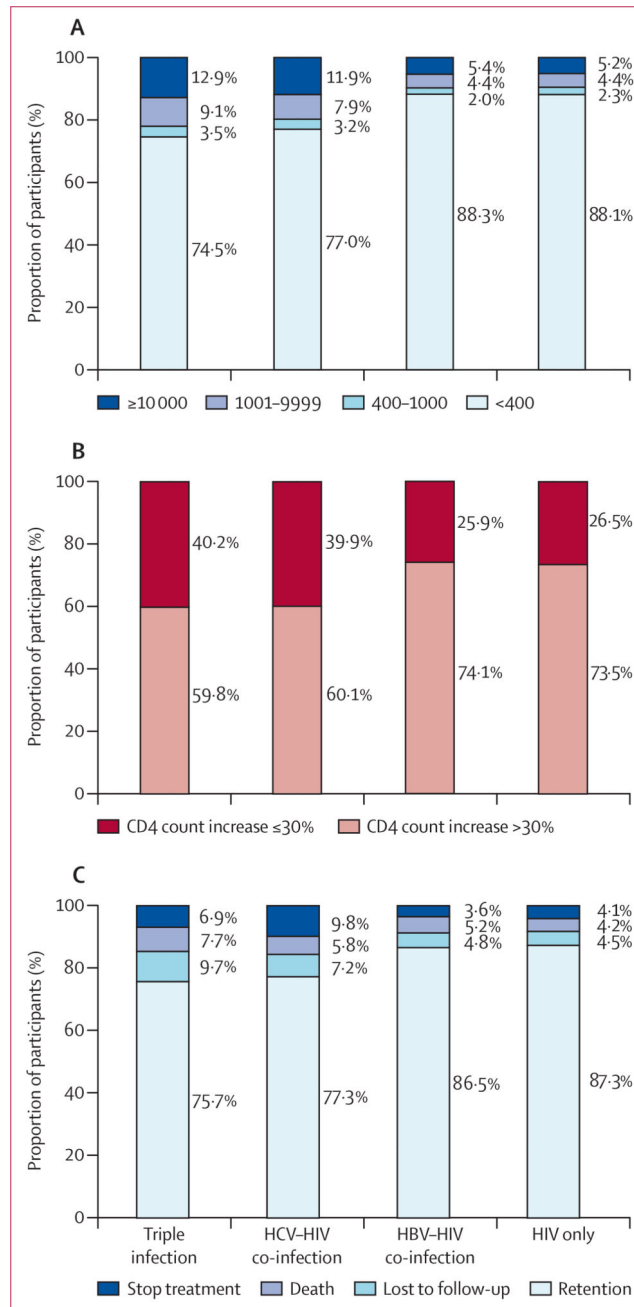


Figure 2. Outcomes after 12 months of combination antiretroviral therapy
 (A) Viral load response, (B) change of CD4 cell count, and (C) retention status.
 HBV=hepatitis B virus. HCV=hepatitis C virus.

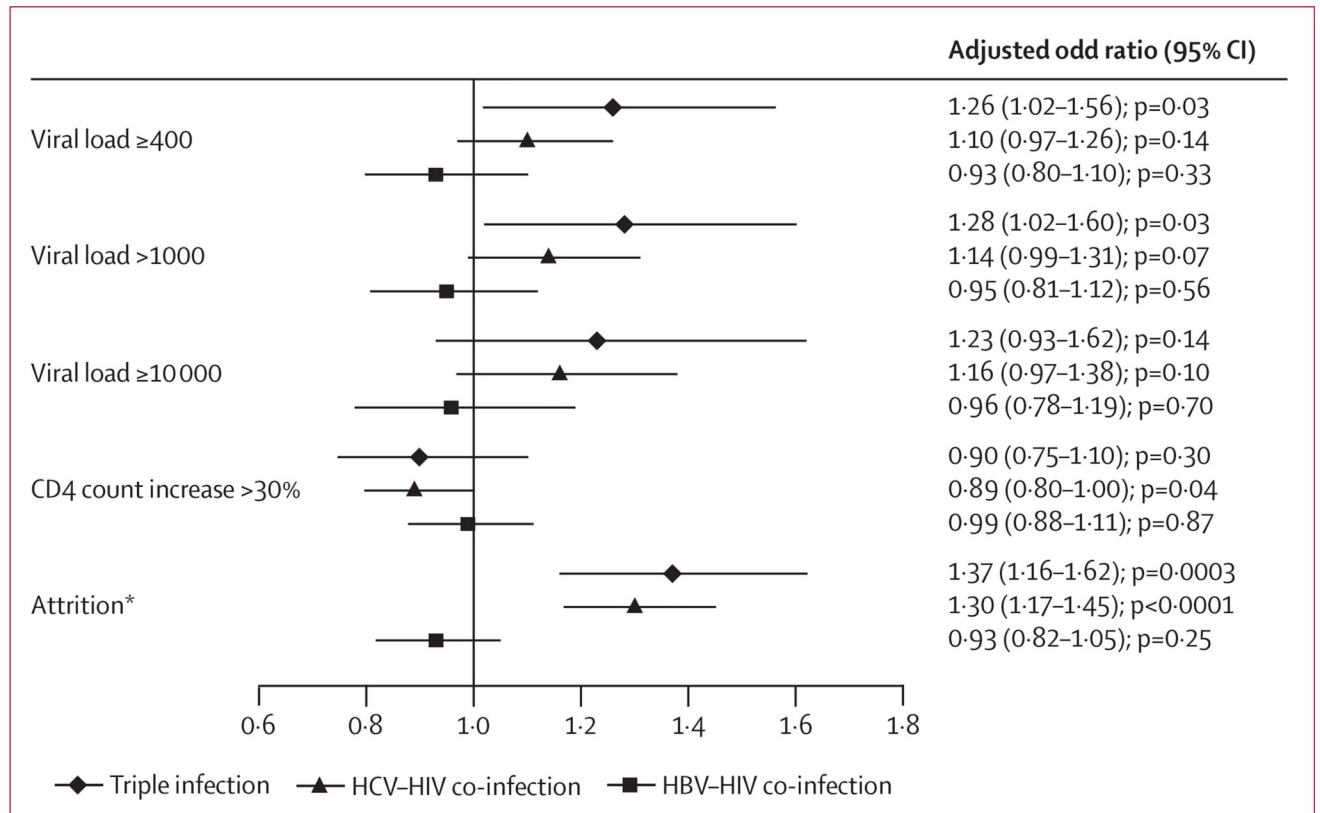


Figure 3. Multivariable analyses of association between hepatitis co-infection and outcomes Controlled for age, sex, treatment centre, CD4 cell count, HIV transmission mode, and initial antiretroviral treatment regimens. *Includes death and stopping.

Table 1

Baseline characteristics

	Total (n=33 861)	Triple infection (n=1114)	HCV-HIV co-infection(n=6149)	HBV-HIV co-infection (n=2958)	HIV only (n=23 640)
Age at start of antiretroviral therapy (years)	37 (31-46)	35 (31-40)	36 (32-41)	37 (31-46)	38 (30-48)
18-24	2135 (6.3%)	33 (3.0%)	188 (3.1%)	180 (6.1%)	1734 (7.4%)
25-29	4854 (14.3%)	146 (13.1%)	699 (11.4%)	439 (14.8%)	3570 (15.1%)
30-34	6354 (18.8%)	324 (29.1%)	1524 (24.8%)	579 (19.6%)	3927 (16.6%)
35-39	6537 (19.3%)	329 (29.5%)	1841 (29.9%)	506 (17.1%)	3861 (16.3%)
40-44	4669 (13.8%)	170 (15.3%)	1188 (19.3%)	402 (13.6%)	2909 (12.3%)
45-54	4887 (14.4%)	90 (8.0%)	574 (9.3%)	461 (15.6%)	3762 (15.9%)
55	4425 (13.1%)	22 (2.0%)	135 (2.2%)	391 (13.2%)	3877 (16.4%)
Sex					
Male	22 534 (66.6%)	942 (84.6%)	4951 (80.5%)	2064 (69.8%)	14 577 (61.7%)
Female	11 327 (33.4%)	172 (15.4%)	1198 (19.5%)	894 (30.2%)	9063 (38.3%)
Transmission mode					
Blood transfusion or previous plasma donation	418 (1.3%)	14 (1.3%)	168 (2.9%)	43 (1.5%)	193 (0.9%)
Injection drug use	6959 (22.0%)	803 (74.8%)	4457 (75.9%)	316 (11.3%)	1383 (6.3%)
MSM	3159 (10.0%)	8 (0.8%)	61 (1.0%)	317 (11.4%)	2773 (12.7%)
Heterosexual	21 128 (66.7%)	248 (23.1%)	1187 (20.2%)	2113 (75.8%)	17 580 (80.1%)
Type of treatment centre					
Infectious disease hospital	2356 (7.0%)	53 (4.8%)	370 (6.0%)	199 (6.7%)	1734 (7.4%)
Provincial or prefectural hospital	11 407 (33.8%)	313 (28.3%)	2017 (33.0%)	1126 (38.3%)	7951 (33.8%)
Center for Disease Control and Prevention	5145 (15.3%)	89 (8.0%)	474 (7.8%)	475 (16.2%)	4107 (17.4%)
County or lower level hospital	14 809 (43.9%)	652 (58.9%)	3253 (53.2%)	1142 (38.8%)	9762 (41.4%)
Baseline CD4 count (cells per µL)	195 (82-283)	223 (110-306)	216 (118-301)	178 (58-271)	190 (74-278)
350	2610 (7.9%)	135 (12.5%)	773 (12.9%)	180 (6.2%)	1522 (6.6%)
200-349	13 547 (40.9%)	459 (42.5%)	2494 (41.8%)	1100 (38.0%)	9494 (40.9%)
50-199	11 054 (33.4%)	341 (31.6%)	2083 (34.9%)	967 (33.4%)	7663 (33.0%)
0-49	5927 (17.8%)	144 (13.4%)	619 (10.4%)	647 (22.4%)	4517 (19.5%)

	Total (n=33 861)	Triple infection (n=1114)	HCV-HIV co-infection (n=6149)	HBV-HIV co-infection (n=2958)	HIV only (n=23 640)
Alanine aminotransferase concentration (U/L)					
<40	24 358 (72.6%)	581 (52.7%)	3338 (54.6%)	1975 (67.4%)	18 464 (78.9%)
40-79	6768 (20.2%)	344 (31.2%)	1800 (29.5%)	711 (24.3%)	3913 (16.7%)
80	2417 (7.2%)	177 (16.1%)	970 (15.9%)	245 (8.4%)	1025 (4.4%)
Total bilirubin concentration (μmol/L)					
<17.1	28 271 (87.0%)	827 (79.4%)	4836 (82.9%)	2410 (83.9%)	20 198 (88.8%)
17.1	4233 (13.0%)	214 (20.6%)	999 (17.1%)	462 (16.1%)	2558 (11.2%)
Initial antiretroviral regimen					
AZT+3TC+NVP/EFV	22 340 (66.0%)	652 (58.5%)	3876 (63.0%)	1646 (55.7%)	16 166 (68.4%)
D4T+3TC+NVP/EFV	8811 (26.0%)	286 (25.7%)	1480 (24.1%)	731 (24.7%)	6314 (26.7%)
TDF+3TC+NVP/EFV	2710 (8.0%)	176 (15.8%)	793 (12.9%)	581 (19.6%)	1160 (4.9%)

Data are median (IQR) or n (%). All variables were significantly associated with hepatitis co-infection groups ($p<0.05$). HBV=hepatitis B virus. HCV=hepatitis C virus. MSM=men who have sex with men. AZT=zidovudine. 3TC=lamivudine. NVP=nevirapine. EFV=efavirenz. D4T=stavudine. TDF=tenofovir.

Table 2

Associations between hepatitis co-infection and time to death

	Triple infection	HCV–HIV co-infection	HBV–HIV co-infection	HIV only
All-cause mortality (n=33 861)				
Number of events	131	501	186	1236
Time on antiretroviral treatment (months)	17 892	96 680	49 007	392 821
Unadjusted HR (95% CI), p value	2.32 (1.94–2.77), <0.0001	1.62 (1.46–1.80), <0.0001	1.21 (1.03–1.41), 0.02	..
HR adjusted by age and sex (95% CI), p value	2.49 (2.07–2.99), <0.0001	1.72 (1.54–1.92), <0.0001	1.20 (1.03–1.40), 0.02	..
HR adjusted by all factors but not transmission mode (95% CI), p value	2.63 (2.16–3.20), <0.0001	2.03 (1.80–2.28), <0.0001	1.09 (0.92–1.29), 0.31	..
HR adjusted by all factors and transmission mode (95% CI), p value	1.90 (1.53–2.37), <0.0001	1.46 (1.25–1.70), <0.0001	1.06 (0.89–1.26), 0.51	..
HR adjusted by all factors, stratified by transmission mode (95% CI), p value	1.63 (1.23–2.17), 0.0008	1.21 (0.97–1.51), 0.09	0.97 (0.61–1.54), 0.91	..
Sexual transmission	1.99 (1.31–3.02), 0.001	1.84 (1.47–2.29), <0.0001	1.04 (0.86–1.26), 0.71	..
Non-injury mortality (n=33 695)				
Number of events	117	450	174	1147
Time on antiretroviral treatment (months)	17 736	96 170	48 906	392 107
Unadjusted HR (95% CI), p value	2.25 (1.86–2.72), <0.0001	1.58 (1.41–1.76), <0.0001	1.22 (1.04–1.43), 0.02	..
HR adjusted by age and sex (95% CI), p value	2.43 (2.00–2.95), <0.0001	1.68 (1.50–1.89), <0.0001	1.21 (1.03–1.42), 0.02	..
HR adjusted by all factors but not transmission mode (95% CI), p value	2.57 (2.09–3.15), <0.0001	2.00 (1.77–2.26), <0.0001	1.09 (0.92–1.29), 0.34	..
HR adjusted by all factors and transmission mode (95% CI), p value	1.94 (1.54–2.44), <0.0001	1.47 (1.25–1.73), <0.0001	1.06 (0.89–1.27), 0.51	..
HR adjusted by all factors, stratified by transmission mode (95% CI), p value	1.68 (1.24–2.27), 0.001	1.25 (0.99–1.59), 0.06	0.96 (0.59–1.58), 0.88	..
Sexual transmission	2.04 (1.33–3.13), 0.001	1.79 (1.42–2.26), <0.0001	1.06 (0.87–1.29), 0.57	..

HBV=hepatitis B virus. HCV=hepatitis C virus. HR=hazard ratio.