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MAJOR ARTICLE

Risk of End-Stage Liver Disease in HIV-Viral Hepatitis Coinfected Persons in North America From the Early to Modern Antiretroviral Therapy Eras

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(See the Editorial Commentary by Wittkop on pages 1168–70.)

Background. Human immunodeficiency virus (HIV)–infected patients coinfected with hepatitis B (HBV) and C (HCV) viruses are at increased risk of end-stage liver disease (ESLD). Whether modern antiretroviral therapy has reduced ESLD risk is unknown.

Methods. Twelve clinical cohorts in the United States and Canada participating in the North American AIDS Cohort Collaboration on Research and Design validated ESLD events from 1996 to 2010. ESLD incidence rates and rate ratios according to hepatitis status adjusted for age, sex, race, cohort, time-updated CD4 cell count and HIV RNA were estimated in calendar periods corresponding to major changes in antiretroviral therapy: early (1996–2000), middle (2001–2005), and modern (2006–2010) eras.

Results. Among 34 119 HIV-infected adults followed for 129 818 person-years, 380 incident ESLD outcomes occurred. ESLD incidence (per 1000 person-years) was highest in triply infected (11.57) followed by HBV- (8.72) and HCV- (6.10) coinfected vs 1.27 in HIV-monoinfected patients. Adjusted incidence rate ratios (95% confidence intervals) comparing the modern to the early antiretroviral era were 0.95 (.61–1.47) for HCV, 0.95 (.40–2.26) for HBV, and 1.52 (.46–5.02) for triply infected patients. Use of antiretrovirals dually activity against HBV increased over time. However, in the modern era, 35% of HBV-coinfected patients were not receiving tenofovir. There was little use of HCV therapy.

Conclusions. Despite increasing use of antiretrovirals, no clear reduction in ESLD risk was observed over 15 years. Treatment with direct-acting antivirals for HCV and wider use of tenofovir-based regimens for HBV should be prioritized for coinfected patients.

Keywords. HIV; hepatitis C virus; hepatitis B virus; coinfection; end-stage liver disease.

It has been estimated that 10 million (30%) human immunodeficiency virus (HIV)–infected persons worldwide are coinfected with chronic hepatitis C virus (HCV) [1] and 3 to 5 million (5%–15%) with chronic hepatitis B virus (HBV) [2, 3]. HIV accelerates liver disease caused by both HBV and HCV and may itself cause liver injury [4]. HIV replication and associated immune dysfunction are correlated with liver disease progression in the setting of coinfection [5], whereas sustained HIV control may reduce liver fibrosis and hepatic decompensation [6, 7]. HIV therapy has evolved so that treatments are now safer, more effective, and widely accessible in the United States and Canada, resulting in most HIV-infected adults in care achieving prolonged HIV suppression, immune reconstitution, and reduced mortality from AIDS [8]. HIV-infected people now survive long enough to develop complications of chronic viral hepatitis, particularly end-stage liver disease (ESLD) and hepatocellular carcinoma, which have become leading causes of morbidity and mortality [9, 10].

The extent to which HIV treatment and viral suppression have reduced the risk of ESLD is not known. HIV therapy itself can have dual activity against HBV. Lamivudine (3TC) suppresses HBV DNA, although resistance develops rapidly and more commonly in HIV-infected patients [11, 12]. However, tenofovir (TDF) with/or without 3TC or emtricitabine (FTC) as part of an HIV treatment regimen can be used to achieve prolonged suppression of HBV DNA and potentially reduce liver disease outcomes [13]. HCV-coinfected patients on combination antiretroviral therapy (ART) appear to remain at increased risk for hepatic decompensation compared with HCV-monoinfected

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patients [7]. Recent advances in HCV therapies have resulted in greater cure rates and have the potential to dramatically reduce the risk of ESLD, although, until recently, these therapies have not been widely used. Understanding how ESLD risk has evolved since the introduction of effective ART is necessary to gauge the potential impact of new HCV therapies.

Our objective in this study was to estimate temporal trends in ESLD among HIV-infected persons with and without HBV and HCV coinfection by calendar periods that correspond to major changes in ART availability, safety, and clinical practice prior to the widespread use of direct-acting HCV therapies.

METHODS

Study Population

The North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) is a consortium of clinical and interval HIV cohorts from Canada and the United States and has been described elsewhere [14]. Briefly, NA-ACCORD consists of 25 cohorts that collect data on more than 150 000 HIV-infected persons engaged in clinical care at more than 200 clinical sites [15]. At scheduled intervals, cohorts securely transfer demographic, medication, laboratory, diagnostic, and vital status information to the central Data Management Core (University of Washington), where data undergo quality control and are harmonized for analyses by the Epidemiology/Biostatistics Core (Johns Hopkins University). The human subject research activities of the NA-ACCORD and each participating cohort have been approved by their respective local institutional review boards and the Johns Hopkins School of Medicine.

All HIV-infected adults aged ≥18 years seeking care in the 12 (10 in United States and 2 in Canada) NA-ACCORD clinical cohorts that participated in a substudy validating ESLD diagnoses from 1 January 1996 to 31 December 2010 were eligible. We excluded prevalent ESLD cases, defined as participants who had validated ESLD prior to or within 3 months of cohort entry.

Outcome: Validated End-Stage Liver Disease

Twelve clinical cohorts used medical record review to validate cases of ESLD as previously described [16]. Criteria for ESLD ascertainment were determined centrally using a screening algorithm developed by the NA-ACCORD, which selected patients with laboratory and/or clinical diagnoses or procedures suggestive of ESLD (ie, paracentesis, liver transplant) to undergo validation for ESLD events [16]. Laboratory criteria included 2 validated noninvasive laboratory-based measures of hepatic fibrosis: the aspartate aminotransferase/platelet ratio index (APRI) [17] and fibrosis-4 (FIB-4) [18] using predefined cutoffs indicative of significant fibrosis (eg, at least 2 APRI scores >1.5 or 2 FIB-4 scores >3.25, more than 6 months apart) *and* at least 1 of the following other laboratory abnormalities that indicate impaired hepatic function: total bilirubin ≥5 mg/dL, albumin <20 g/L, or an international normalized ratio >1.7. Diagnostic criteria included any single clinician-documented diagnostic or procedure code consistent with ESLD [16]. Each potential case identified then underwent validation for ESLD by review of all available medical records by (or under the supervision of) a physician at each cohort. A centralized web-based application was used to standardize ESLD data collection and confirm evidence of 1 of the following diagnoses: ascites, spontaneous bacterial peritonitis, variceal hemorrhage, hepatic encephalopathy, or hepatocellular carcinoma. The earliest confirmed diagnosis date of ESLD was used.

Exposures: Hepatitis B and C Infection

HBV infection was defined by the presence of a positive hepatitis B surface antigen, hepatitis B e antigen, or a detectable hepatitis B DNA result measured at any time while under observation. HCV infection was defined as a positive HCV antibody or detectable HCV RNA or genotype result measured at any time while under observation. Both HBV and HCV infections were measured as time-fixed variables due to the likelihood that the infection occurred around the time of HIV infection (which would be prior to entry into the NA-ACCORD), regardless of when documentation of HBV or HCV status occurred. Triply infected patients were HIV-, HBV-, and HCV-infected.

Covariates of Interest

Race (black, white, or other/unknown) and history of injection drug use (IDU) were self-reported at enrollment into the local cohort. ART was defined as a combination of 3 antiretroviral agents from at least 2 classes or a triple nucleoside/nucleotide reverse transcriptase inhibitor regimen containing abacavir or TDF. ART exposure was time updated in each calendar period (below). Exposure to ART and to medications with specific HBV activity—3TC, FTC, and TDF—was assessed as having any use for a period of at least 1 month in a given treatment era.

We defined 3 periods of calendar time of interest: the early (1996–2000), middle (2001–2005), and modern (2006–2010) ART eras, which roughly correspond to when major changes in ART regimens (eg, safety, tolerability, and effectiveness) and clinical practice took place. For example, 2001 guidelines changed to recommend treating all patients with CD4 < 350 cells/mm^3 [19] and, in 2004, HCV and HBV-coinfected patients were first recognized as constituting special populations [20]. TDF received US Food and Drug Administration approval in 2001 [21], and TDF combined with lamivudine (3TC) or/emtricitabine (FTC) was first recommended as the preferred nucleoside backbone for treating HIV in patients coinfected with HBV in 2006 [22].

Due to changes in the sensitivity of HIV RNA assays during the study period, HIV suppression was defined as <500 copies/mL, with each individual's minimum HIV RNA measure selected in each of the time periods.

Heavy alcohol use was defined as ever having been reported while in the NA-ACCORD: ≥3 drinks on any day or ≥7 drinks per week for females and ≥4 drinks on any day or ≥14 drinks per week for males. Individuals from cohorts that did not provide alcohol information were classified as not assessed (63%).

Statistical Analyses

Person-time and ESLD events accrued from baseline to study exit. Baseline was defined as enrollment into the NA-ACCORD, the start of the ESLD observation window for the patient's cohort (defined as the period of time during which ESLD events are believed to be 100% ascertained for each cohort), or 1 January 1996, whichever occurred last. Study exit was defined as ESLD diagnosis date, death date, 1 year after the date of the patient's last CD4 or HIV RNA (as a measure of loss to follow-up), the end of the ESLD observation window for the patient's cohort, or 31 December 2010, whichever occurred first.

Poisson regression models were used to estimate adjusted ESLD incidence rates (IRs) per 1000 person-years and incidence rate ratios (IRRs) with associated 95% confidence intervals (CIs) in each of the ART eras according to HBV and HCV status. IRRs were adjusted for age group (<40, 40–49, 50–59, 60–69, and ≥70 years), sex, race, cohort, and time-updated CD4 cell count and HIV RNA suppression (HIV RNA <500 copies/mL), a surrogate marker for the effectiveness of ART, in each era.

The competing risk of death (eg, from AIDS) may have precluded more ESLD events in the early and middle ART eras vs the modern ART era. We therefore conducted a sensitivity analysis to estimate the probability of ESLD at specific times (2.5, 5, 7.5, and 10 years after study entry) from the parametric cumulative incidence functions of ESLD by HBV and HCV status and by ART era after accounting for the competing risk of death [23] to determine the effect of declining mortality among HIV-infected adults during the study period (1996–2010). Deaths were ascertained through clinical records, matching to provincial registries, the US National Death Index, and the Social Security Death Index.

All analyses were performed using SAS version 9.4 (Carey, North Carolina).

RESULTS

Study Population Characteristics

Of 41 405 HIV-infected patients followed in the 12 cohorts participating in the ESLD validation, 34 119 (82%) met inclusion criteria (see Supplementary Figure 1). Overall, 6347 (19%) patients had documented coinfection with HCV only, 1696 (5%) with HBV only, and 533 (2%) were triply infected. Among the 6880 patients with HCV (with or without HBV), 92% had a positive HCV antibody test, 63% had an HCV RNA test result (of whom 91% were detectable), and 24% had an HCV genotype test; 37% were identified as HCV infected based solely on an HCV antibody positive test. HBV DNA was available in only 40% of those classified as HBV infected. Overall, 380 individuals developed a validated ESLD event during 129 818 person-years of follow-up (IR = 2.9; 95% CI, 2.7, 3.2 per 1000 person-years). The median follow-up was 2.9 years (interquartile range, 1.4, 5.6).

Baseline characteristics of patients are shown in Table 1, stratified by ESLD status. Patients developing ESLD were older, more likely to be male, white, have a history of IDU, be infected with HCV and/or HBV, have baseline APRI score >1.5, an FIB-4 score >3.25, CD4 cell count <200 cells/μL, and detectable HIV RNA. Overall, the proportion of patients with liver fibrosis by either measure did not vary by calendar period. In the subset of patients with alcohol use data, patients developing ESLD were also more likely to report heavy alcohol use.

End-Stage Liver Event Rates and Trends Over Time

The most frequent first ESLD diagnosis observed was ascites (n = 274, 72%) followed by hepatic encephalopathy (n = 43, 11%), variceal hemorrhage (n = 37, 10%), hepatocellular carcinoma (n = 24, 6%), and spontaneous bacterial peritonitis (n = 2, 1%). There were no apparent differences in the types of incident ESLD events reported by either hepatitis status or ART era (see Supplementary Table 1).

Overall, the highest rates of ESLD were observed in those triply infected, followed by those coinfected with HBV, then coinfected with HCV. Rates were substantially lower in HIV-monoinfected patients in all ART eras (Figure 1 and Supplementary Table 2). There was no evidence that ESLD event rates changed appreciably over time nor among any category of hepatitis infection, except possibly for a decrease in ESLD incidence among those infected with HBV in the modern ART era compared with earlier eras. A comparison of adjusted IRR for ESLD between ART eras is shown in Table 2. There was no evidence that ART era modified the effect of viral coinfection status on ESLD incidence (test for interaction, $P = .66$).

Role of Antiviral Therapy

Increasing rates of HIV RNA suppression were observed over calendar time, reaching 85% overall in the modern ART era with no difference in suppression by hepatitis infection status (Figure 2).

There was essentially no recorded use of HCV treatment during the period of study (85 patients, 1%). The use of anti-HBV active agents, however, increased substantially over time. TDF use in particular increased dramatically starting in the middle ART era (2001), reaching 71% in the modern ART era overall (78% among those with HBV and 74% among those triply infected; Figure 3). Of those with HBV infection, 73% were receiving ART in the modern ART era, of whom only 4% were not receiving TDF, 3TC, or FTC. Taken together, 35% of HBV-infected (alone or triply) individuals were not receiving TDF in the modern ART era.

Table 1. Baseline Characteristics Stratified by End-Stage Liver Disease, NA-ACCORD, January 1996–December 2010

Characteristic	No ESLD (N = 33 739) n (%)	ESLD (N = 380) n (%)
Age (y)		
<40	16 615 (49)	145 (38)
40–49	11 853 (35)	144 (38)
50–59	4302 (13)	72 (19)
60–69	840 (2)	17 (4)
≥70	129 (0)	2 (1)
Male	26 559 (79)	325 (86)
Race		
White	13 763 (41)	186 (49)
Black	11 955 (35)	122 (32)
Other/unknown	8021 (24)	72 (19)
History of injection drug use	4842 (14)	109 (29)
Hepatitis status		
Hepatitis B infection only	1640 (5)	56 (15)
Hepatitis C infection only	6174 (18)	173 (46)
Hepatitis B and C infection	506 (1)	27 (7)
Hepatitis B uninfected and C uninfected	18 649 (55)	92 (24)
Not assessed	6770 (20)	32 (8)
Heavy alcohol use		
Never	5616 (17)	45 (12)
Ever	6867 (20)	133 (35)
Not assessed	21 256 (63)	202 (53)
APRI score >1.5	1104 (3)	88 (23)
FIB-4 score >3.25	1104 (3)	91 (24)
CD4 < 200 cells/mm^3	8646 (26)	146 (38)
HIV RNA ≥500 copies/mL	18 620 (55)	226 (59)
History of clinical AIDS diagnosis	7111 (21)	90 (24)
ART regimen		
ART naïve	20 520 (61)	242 (64)
Protease inhibitor–based regimen	8309 (25)	106 (28)
Nonnucleoside reverse transcriptase inhibitor–based regimen	4210 (12)	24 (6)
Other	700 (2)	8 (2)

Sex, race/ethnicity, and HIV transmission risk factor were collected at enrollment into the NA-ACCORD and are time fixed. Age was measured as year of baseline – year of birth. Not assessed was measured as lacking the necessary data to measure either hepatitis B virus, hepatitis C virus, or both. Heavy alcohol use was defined as ever having reported while under observation in the NA-ACCORD: ≥3 drinks on any day or 7 drinks per week for females and ≥4 drinks on any day or 14 drinks per week males. Individuals from cohorts that did not provide alcohol information were classified as not assessed. Aspartate aminotransferase/platelet ratio index (APRI), a surrogate for liver fibrosis is calculated as: [(AST level, in IU/L/AST upper limit of normal, in IU/L)/platelet count, in 10^9/L)] * 100. APRI was estimated using AST and platelet measurements made at, or prior to, baseline. FIB-4 is an alternate noninvasive score to estimate the amount of liver fibrosis, calculated as: (age, in years) * (AST level, in IU/L)/(platelet count, in 10^9/L) * (square root ALT, in IU/L). FIB-4 was estimated using AST, ALT, and platelet measurements made at, or prior to, baseline. CD4 count and HIV RNA were measured as close to baseline as possible, within a window period of 6 months before to 6 months after baseline. History of clinical AIDS diagnoses was defined by *International Classification of Diseases, Ninth Revision, Clinical Modification* codes for AIDS-defining illnesses, including pneumocystis pneumonia, tuberculosis, mycobacterium, cytomegalovirus, HIV wasting, HIV dementia, candidiasis, cryptococcosis, toxoplasmosis of the brain, coccidiomycosis, histoplasmosis, isosporiasis, herpes zoster, herpes simplex, bacterial pneumonia, or Kaposi sarcoma; history of clinical AIDS diagnosis was measured at, or prior to, baseline. ART was measured as a combination of 3 antiretroviral agents from at least 2 classes or a triple nucleoside/nucleotide reverse transcriptase inhibitor regimen containing abacavir or tenofovir.

Abbreviations: ART, antiretroviral therapy; AST, aspartate aminotransferase; ESLD, end-stage liver disease; FIB-4, fibrosis-4; HIV, human immunodeficiency virus; NA-ACCORD, North American AIDS Cohort Collaboration on Research and Design.

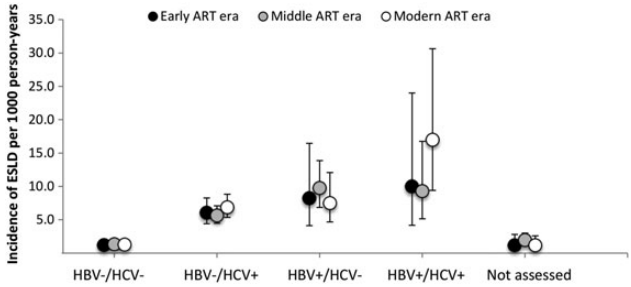

Figure 1. End-stage liver disease (ESLD) incidence rates and 95% confidence intervals by viral hepatitis coinfection status and antiretroviral therapy (ART) era, North American AIDS Cohort Collaboration on Research and Design, January 1996–December 2010. Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus.

Sensitivity Analysis

As expected, mortality rates were highest in the early ART era and fell by approximately half by the modern ART era (see Supplementary Figure 3). The cumulative incidence functions of ESLD after accounting for the competing risk of death did not differ over time within each HBV/HCV status group (see Supplementary Figure 4*A*–*D*), suggesting minimal impact of the decreasing competing risk of death on the incidence of ESLD over time.

DISCUSSION

With more than 34 000 persons followed for 15 years, this study is the largest and longest prospective evaluation of validated ESLD outcomes conducted in an HIV-infected population. ESLD events were common in all time periods studied and occurred more frequently among those with viral hepatitis coinfection but were also observed in patients infected with only HIV. Patients triply infected with HIV, HCV, and HBV were at particularly high risk, having a 12-fold higher incidence rate of ESLD compared with HIV-monoinfected patients, even in the modern ART era. Even after accounting for competing risks of death, CD4, and HIV RNA suppression, we observed no apparent improvement in ESLD rates in our HIV/HCV-coinfected population.

Effective control of HIV replication has been shown to reduce hepatic inflammation and fibrosis progression in the setting of HIV coinfection in the short term [24]. There is some evidence that liver-related morbidity and mortality have declined in more recent calendar periods in some studies [25, 26] but not others [27]. Reduced hepatic decompensation events in HIV/HCV-coinfected men initiating ART compared with those never receiving ART supports individual benefit of ART on ESLD risk (adjusted hazard ratio, 0.72; 95% CI, .54–.94) [6]. This reduction, however, could be partly counterbalanced by a reduction in the competing risk of death from AIDS, creating a stalemate in

Table 2. Adjusted Incidence Rate Ratios and 95% Confidence Intervals of End-Stage Liver Disease in the Modern (2006–2010) and Middle (2001–2005) vs Early (1996–2000) and Modern vs Middle Antiretroviral Therapy Eras, North American AIDS Cohort Collaboration on Research and Design, January 1996–December 2010

	Modern vs Early ART Era		Modern vs Middle ART Era		Middle vs Early ART Era	
Viral Hepatitis Status	aIRR	95% CI	aIRR	95% CI	aIRR	95% CI
Overall	0.98	.72, 1.33	0.97	.77, 1.22	1.01	.76, 1.35
HBV-, HCV-	1.24	.63, 2.31	1.03	.66, 1.61	1.21	.63, 2.31
HCV+ only	0.95	.61, 1.47	1.12	.79, 1.58	0.85	.57, 1.27
HBV+ only	0.95	.40, 2.26	0.69	.38, 1.26	1.37	.62, 3.01
HBV+, HCV+	1.52	.46, 5.02	1.88	.79, 4,45	0.81	.25, 2.60
HBV and HCV not assessed	1.29	.37, 4.49	0.71	.28, 1.82	1.81	.66, 4.93

Incidence rate ratios were estimated using a Poisson regression model stratified by hepatitis B virus (HBV) and hepatitis C virus (HCV) status and adjusted for age, sex, race, cohort and time-varying CD4 and human immunodeficiency virus RNA.

Abbreviations: aIRR, adjusted incidence rate ratio; ART, antiretroviral therapy; CI, confidence interval.

ESLD rates over time. Nonetheless, HIV/HCV-coinfected patients continue to have higher rates of hepatic decompensation than HCV-monoinfected patients [7]. Chronic toxicity of ART, persistent immune dysfunction, and ongoing substance use may all contribute to the residual increased risk of liver disease. Thus, while ART is beneficial, it is clear that HIV control alone will be ineffective at reducing ESLD and that HCV therapy will be needed.

Although data on coinfection are still limited, HCV-monoinfected patients who are cured after HCV treatment have improved survival, comparable with that of the general population [28]. In the NA-ACCORD during the period under study, there appeared to be minimal use of HCV treatment. This is consistent with overall low treatment rates in the United States and Canada (less than 10% in HCV overall [29], 4% in coinfected veterans [6], and <1% in IDUs [30]) during the interferon treatment era. The advent of safe and effective, all-oral, direct-acting antivirals (DAAs) has the potential to dramatically affect the natural history of HCV in coinfection [31]. However, concerted efforts are needed to address barriers to DAA use, such as high treatment costs, complexities of obtaining reimbursement, and ongoing active substance use, in order to broaden treatment access and ensure wide uptake in this priority population [13]. It will be important to assess the extent to which DAAs will impact the high rates of ESLD

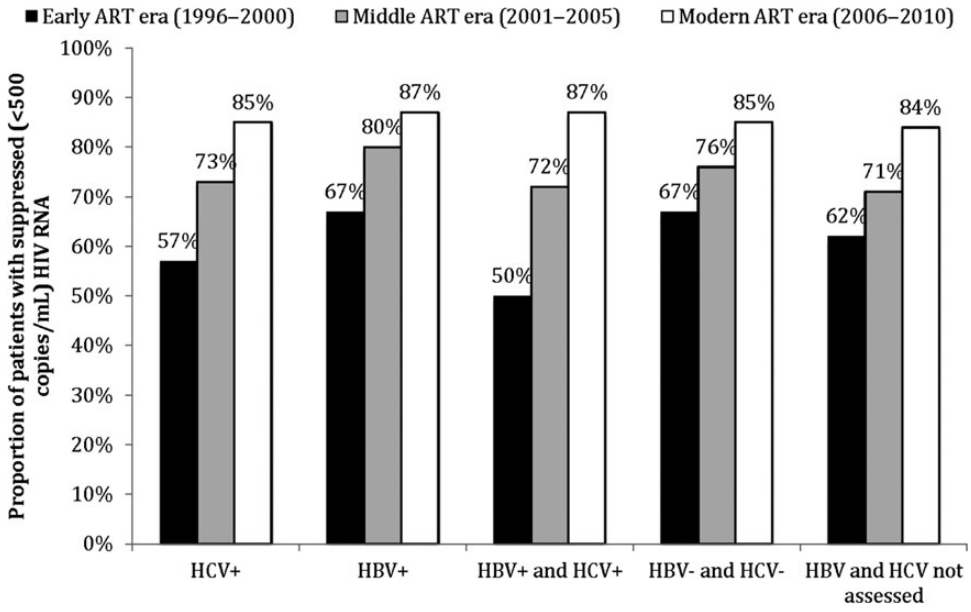

Figure 2. Human immunodeficiency virus (HIV) RNA suppression by viral hepatitis coinfection status and antiretroviral therapy (ART) era, North American AIDS Cohort Collaboration on Research and Design, January 1996–December 2010. Notes: HIV RNA suppression was defined as <500 copies/mL. Each patient's minimum HIV RNA measurement was selected in the time periods. The denominator for the proportions included all patients under observation during that time period, based on baseline and study exit. Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus.

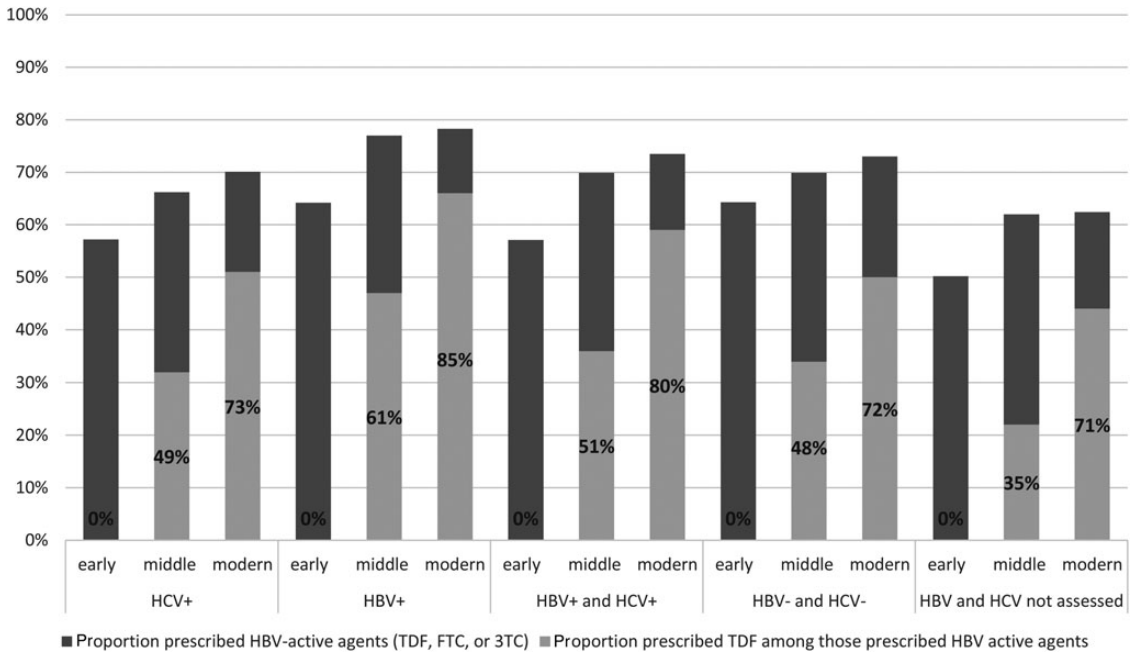

Figure 3. Prescription of hepatitis B virus (HBV)-active antiretroviral therapies (ART; dark gray bars) overlayed with the proportion prescribed tenofovir among those receiving HBV-active therapy (light gray bars), by viral hepatitis coinfection status and ART era, North American AIDS Cohort Collaboration on Research and Design, January 1996–December 2010. Proportion prescribed HBV-active ART represents the number of those prescribed HBV-active agents (tenofovir [TDF], lamivudine [3TC], and emtricitabine [FTC])/the number of those prescribed ART. The proportion prescribed TDF represents the number of those prescribed TDF/the number of those prescribed HBV-active ART and is additionally displayed as a percentage overlying the bars. Abbreviation: HCV, hepatitis C virus.

among coinfected patients as these treatments become used more widely in North America.

The additional impact of long-term HBV viral control through the dual activity of nucleos(t)ide analogs would be expected to reduce complications related to chronic HBV infection. HBV suppression has been shown to reduce liver-related outcomes in HBV monoinfection [32, 33] and to reduce hepatic decompensation in triply infected patients [34]. However, there are little long-term data on the impact of HBV DNA suppression on liver disease progression in HIV coinfection.

When comparing the early to the middle ART era (when TDF was approved), TDF uptake increased dramatically; however, no appreciable change in the rates of ESLD events were observed among HBV-infected persons. There is some suggestion that ESLD events were decreasing in the modern ART era (40% lower than in the early ART era), although given the relatively few events observed, the lower bound of the 95% CI was consistent with no change. The HBV-infected group was in fact the only one to show any such reduction in ESLD, suggesting that HBV suppression associated with anti-HBV active ART indeed may lead to reduced event rates but that its impact may take years to be achieved.

One reason for continued high ESLD rates among HIV/HBV patients in the modern ART era may be that a large proportion (35%) were not actually receiving optimal HBV suppressive therapy with TDF. In fact, 27% of HBV-coinfected patients were not receiving any therapy for HIV despite guideline recommendations that all HIV/HBV-infected patients be considered for HIV treatment [22]. This clearly represents a missed opportunity for ESLD prevention. HBV therapy also may not be fully effective in the setting of HIV. A large proportion of HIV/HBV-coinfected patients fail to achieve HBV DNA suppression despite use of TDF-based ART [35, 36]. In coinfected patients with prior 3TC experience receiving TDF and FTC/3TC, HBV DNA was detected in 20% of follow-up visits over 2 years [37]. In patients receiving TDF for more than 6 years, 10% had persistent, low-level HBV detected despite adequate adherence; however, the clinical consequences of ongoing viral replication were unclear [38].

Finally, HIV-monoinfected patients were not spared ESLD. Comorbidities that impact liver disease are widespread in the population, including alcohol use and fatty liver disease, in part, due to long-term ART toxicity. This should be the focus of future investigation, especially as the HIV-infected population continues to age with effective ART [39].

The NA-ACCORD comprises a large number of HIV- and viral hepatitis–coinfected individuals with wide geographic distribution in the United States and Canada and is broadly representative of the demography of the epidemic in the United States [15]. We used stringent validation methods for ESLD and accounted for competing risks of death. However, several potential limitations are worthy of consideration. Given missing

data, we were not able to classify all patients with hepatitis. However, ESLD rates among those without available hepatitis serology were very similar to rates among those monoinfected with HIV. Lack of HCV RNA and HBV DNA testing in the majority precluded confirmation of chronic infection in all who were categorized as having viral hepatitis. Our results, therefore, are likely to be conservative, as a proportion may have cleared their viral hepatitis infection spontaneously or through treatment. Lack of complete data on alcohol use is a potential limitation. However, at-risk alcohol use was common in both HIV-monoinfected and -coinfected patients (50% and 60%–70%, respectively) and was stable over the study period and therefore is unlikely to be a confounder. The ART exposure measure used was relatively crude (any use recorded in the time period) and may have overestimated the actual time on HBV suppressive therapy. The lack of HBV DNA measures also prevented us from determining how effective these therapies were at controlling HBV infection.

In conclusion, HIV-infected patients coinfected with HBV or HCV are at markedly increased risk for ESLD compared with those infected with HIV alone. The continued high incidence of ESLD despite modern ART underscores the urgent need to specifically address HCV and HBV infections in HIV infected adults. Improved identification, staging, monitoring, and treatment of coinfected persons should be prioritized.

Supplementary Data

Supplementary materials are available at http://cid.oxfordjournals.org. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

Author contributions. M. B. K. and K. N. A. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: M. B. K., K. N. A., Y. J., V. L. R., G. D. K., M. K., M. H., H. N. K., E. M., M. J. S., T. R. S., J. E. T., S. N., J. E., M. J. G., M. G. P., A. M., E. R. C., and R. M. Acquisition of data: M. B. K., K. N. A., M. K., V. L. R., G. D. K., M. J. S., T. R. S., J. E. T., S. N., J. E., M. J. G., A. J., and R. M. Analysis and interpretation of data: M. B. K., K. N. A., Y. J., and B. L. Drafting of the manuscript: M. B. K., K. N. A., and Y. J. Critical revision of the manuscript for important intellectual content: M. B. K., B. L., V. L. R., G. D. K., M. H., H. N. K., G. S., E. M., M. J. S., T. R. S., J. E. T., A. C., S. N., J. E., M. J. G., A. J., M. G. P., J. G., A. M., C. L. T., E. R. C., and R. M. Statistical analysis: K. N. A. and Y. J. Obtained funding: R. M. Administrative, technical, or material support: M. B. K., K. N. A., M. K., and R. M. Study supervision: M. B. K., K. N. A., and R. M.

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APPENDIX

Additional Contributions

NA-ACCORD Collaborating Cohorts and Representatives

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