HIV AND HEPATITIS B CO-INFECTION: RECENT IMPROVEMENTS IN SHORT-TERM MORTALITY AND EFFECT OF MODERN THERAPY ON HIV OUTCOMES

Sarah M. Radke

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Approved by:

Sonia Napravnik, MSPH, PhD
Joseph J. Eron, Jr., MD
Stephen R. Cole, PhD
Mark S. Sulkowski, MD
Steven Meshnick, MD, PhD
ABSTRACT

Sarah Radke: HIV and Hepatitis B Co-infection: Recent Improvements in Short-term Mortality and Effect of Modern Therapy on HIV Outcomes
(Under the direction of Sonia Napravnik)

Hepatitis B virus (HBV) co-infection increases morbidity and mortality among HIV-infected individuals. US treatment guidelines recommend initial antiretroviral therapy (ART) for HIV/HBV co-infected patients include agents active against both HIV and HBV, in particular tenofovir disoproxil fumerate (TDF), based on its efficacy against HBV outcomes. Few studies have examined the comparative effectiveness of TDF-containing ART regimens versus regimens without TDF on HIV outcomes in co-infected patients. To examine the relationship between HBV co-infection and all-cause mortality, we examined data on 3,706 HIV-infected individuals enrolled in the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) who began ART during three periods: 1998-2001, 2002-2004 and 2005-2008. Time to mortality hazard ratios comparing HBV-infected and HBV-uninfected patients were 2.20 (95% Confidence Interval [CI]: 0.92, 5.23), 2.09 (95% CI: 0.86, 5.07) and 0.96 (95% CI:0.29, 3.16) for patients initiating therapy in 1998-2001, 2002-2004 and 2005-2008 respectively, adjusted for baseline demographic and clinical characteristics. To examine the effect of TDF on HIV virologic and immunologic response, we examined the 212 (6%) HBV co-infected patients in the CNICS cohort. TDF use was associated with superior HIV RNA response during the first 19 months of ART, with an adjusted hazard ratio for time to HIV virologic failure comparing patients without TDF use to patients with TDF use of 2.26 (95% CI: 1.1.8, 4.34). No effect of TDF use on time to HIV virologic failure was seen after
patients had consistent HIV RNA suppression for more than 19 months (adjusted hazard ratio=0.44, 95% CI: 0.15, 1.31). We did not observe an effect of TDF use on CD4 count response. Our findings help in identifying the optimal therapeutic management of HIV/HBV co-infected patients, which is not only relevant to individuals living in the US, but is also increasingly relevant to areas of the world where HBV is endemic and modern ART is increasingly available. Efforts to expand the use of agents efficacious against both HIV and HBV are needed, as well as careful monitoring to ensure the positive benefits seen in our studies are also seen for HIV/HBV co-infected patients living in resource limited settings.
For Patric,
Waiho i te toipoto, kaua i te toiroa.
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<thead>
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<th>Description</th>
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<tr>
<td>3TC</td>
<td>Lamivudine</td>
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<tr>
<td>APRI</td>
<td>Aspartate Aminotransferase-to-Platelet Ratio Index</td>
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<tr>
<td>ART</td>
<td>Antiretroviral Therapy</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate Aminotransferase</td>
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<tr>
<td>AZT</td>
<td>Zidovudine</td>
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<tr>
<td>CD4</td>
<td>Cluster of Differentiation 4</td>
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<tr>
<td>CFAR</td>
<td>Centers for AIDS Research</td>
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<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>CNICS</td>
<td>Centers for AIDS Research Network of Integrated Clinical Systems</td>
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<tr>
<td>D4T</td>
<td>Stavudine</td>
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<tr>
<td>dL</td>
<td>Deciliter</td>
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<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
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<tr>
<td>EMM</td>
<td>Effect Measure Modification</td>
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<tr>
<td>EMR</td>
<td>Electronic Medical Record</td>
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<tr>
<td>FTC</td>
<td>Emtricitabine</td>
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<td>HBsAg</td>
<td>Hepatitis B Surface Antigen</td>
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<td>HBV</td>
<td>Hepatitis B Virus</td>
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<td>Hepatitis D Virus</td>
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<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
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<tr>
<td>HR</td>
<td>Hazard Ratio</td>
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IgG  Immunoglobulin G
IgM  Immunoglobulin M
IU   International Units
IQR  Interquartile Range
IVDU Intravenous Drug User
L    Liter
LdT  Telivudine
mg   Milligram
mL   Milliliter
mm   Millimeter
MSM  Men Who Have Sex with Men
NNRTI Non-nucleoside(tide) Reverse Transcriptase Inhibitor
NRTI Nucleoside(tide) Reverse Transcriptase Inhibitor
PI   Protease Inhibitor
PI/r Ritonavir-boosted Protease Inhibitor
RNA Ribonucleic Acid
RR   Relative Risk
SAS® Statistical Analysis Software
TDF Tenofovir Disoproxil Fumerate
US   United States
CHAPTER ONE: SPECIFIC AIMS

Human immunodeficiency virus (HIV)/hepatitis B (HBV) co-infected individuals may have inferior response to therapy and long-term clinical outcomes compared to HIV-infected individuals. The widespread use of modern antiretroviral therapy (ART) has substantially decreased HIV-related morbidity and mortality, and non-AIDS events, including liver-related complications caused by HBV infection, are increasingly important to HIV clinical care. Additionally, ART may have unintended effects including hepatotoxicity which may be higher among HBV co-infected individuals. On the other hand, some antiretroviral agents, in particular tenofovir disoproxil fumerate (TDF), emtricitabine (FTC) and lamivudine (3TC), have activity against both HIV and HBV, and when included as part of ART may mitigate HBV-induced liver damage. While the effect of HIV on HBV has been well elucidated (HIV affects HBV by increasing the risk of liver disease and hepatocellular carcinoma, and the rate of HBV reactivation), the impact of HBV on the progression of HIV and response to therapy remains debated.

We assessed the effect of HBV co-infection on time to all-cause mortality. Further, among HIV/HBV co-infected individuals, we examined whether, and to what extent, TDF affects response to initial ART, specifically HIV RNA suppression and CD4 count response. We used data from the Centers for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) study, which is a large HIV clinical cohort including eight sites across the
United States. Our specific aims were:

**Specific Aim 1**

**Among ART-naïve HIV-infected individuals, assess the impact of HBV co-infection on time to mortality.**

a. **Compare demographic and clinical characteristics by HBV co-infection status.**

Independent predictors of HBV co-infection at time of ART initiation were assessed using multivariable log-linear binomial regression. Patient demographic and clinical characteristics at ART initiation considered as potential predictors were age, sex, race/ethnicity, HIV risk transmission group, year of ART initiation, initial ART regimen anchor drug, AIDS defining clinical condition, hepatitis C virus (HCV) co-infection status, aspartate aminotransferase (AST)-to-platelet ratio index (APRI) score, HIV RNA level, CD4 count, creatinine level and CNICS site.

b. **Determine differences in time to mortality by HBV co-infection status stratified by calendar interval of therapy initiation.** HBV co-infection was defined as a positive hepatitis B surface antigen (HBsAg) or HBV DNA result prior to beginning therapy. Mortality included deaths from any cause. Calendar time was divided into three intervals: 1998-2001; 2002-2004; and 2005-2008. Multivariable Cox proportional hazard models were fit for each calendar interval, adjusting for the variables listed above in aim 1a.

**Hypothesis:** HIV/HBV co-infected patients compared to HIV mono-infected patients will be older, more likely to be men who have sex with men (MSM), have a history of intravenous drug use (IVDU) and HCV co-infection, and have higher APRI levels. HBV co-infection will
be associated with a higher risk of death and shorter time to mortality, but this risk will decrease over calendar time.

**Specific Aim 2**

Among ART-naïve HIV/HBV co-infected patients, assess response to ART by TDF receipt.

a. **Compare demographic and clinical characteristics by TDF receipt.** Independent predictors of TDF use were assessed using multivariable log-linear binomial regression. Patient demographic and clinical characteristics considered as potential predictors are listed above in aim 1a.

b. **Evaluate HIV virologic and immunologic response to ART by TDF receipt.** Our main exposure was inclusion of TDF in initial ART, either alone or in combination with FTC or 3TC. HIV virologic failure was defined as having two successive HIV RNA values >400 copies/mL after 16-weeks of ART exposure. The first date where HIV RNA was >400 copies/mL was used as the date of HIV virologic failure. Multivariable Cox proportional hazard models were fit adjusting for the variables listed above in aim 1a. Linear regression fit with generalized estimating equations was used to estimate the association between TDF use and CD4 count response.

**Hypothesis:** HIV/HBV co-infected patients who received TDF (either TDF alone or in combination with 3TC or FTC) will have superior virologic and immunologic outcomes compared to patients who received ART regimens not including TDF.
CHAPTER TWO: BACKGROUND AND SIGNIFICANCE

HIV Infection

HIV infection remains a leading cause of illness and death in the United States. Among the 40 million people in the world infected with HIV/AIDS, there are approximately 1.1 million people infected in the United States, where it is estimated that 56,000 new cases occur annually. HIV increasingly affects women, racial and ethnic minorities and those who acquire HIV through heterosexual contact. HIV is transmitted between individuals by percutaneous or mucous membrane exposure to infective blood or other body fluids. Since the introduction of ART in 1996, HIV-infected individuals are living longer and experiencing more non-AIDS defining illnesses. As a result, liver disease has arisen as an important source of morbidity and mortality among the HIV-infected population.

Hepatitis B Infection

HBV infection is widespread, yet largely goes unreported. Like HIV, HBV is transmitted via body fluids, but HBV is 50-100 times more infectious than HIV. Two billion people worldwide have been infected with HBV and nearly 400 million live with chronic infection. Overall 800,000 to 1.4 million individuals in the United States are living with chronic HBV infection. In the US, the incidence of HBV has declined steadily since the 1980s due to the introduction of the HBV vaccine, which became part of the routine immunization schedule in 1991. The incidence of HBV dropped from 8.5 cases per 100,000
in 1990 to 2.8 cases per 100,000 in 2002. However, because HBV infection is often asymptomatic and may go unreported, the actual number of new infections is estimated to be approximately tenfold higher (figure 2.1). HBV is most common among adults 25-44 years old.

Acute HBV infection rarely leads to long-term morbidity, but chronic HBV leads to significant morbidity and mortality. Less than 1% of acute HBV patients develop liver failure. Resolution of the infection is achieved if an adequate immune response is mounted. However, individuals with a weak or ineffective immune response may develop chronic HBV. In chronically infected patients, the continued expression of inflammatory cytokines and recruitment of activated lymphomononuclear cells to the liver result in fibrosis, cirrhosis and hepatocellular carcinoma (HCC). Liver damage is not caused by the direct action of the HBV, but rather by the immune response against the viral antigens. In other words, liver disease is related to cell-mediated immunity and inflammation rather than being directly cytopathic for hepatocytes. How quickly liver damage progresses depends on patients’ age, gender, immune status and on environmental factors.

Fibrosis, cirrhosis and HCC are more likely to lead to death in HBV-infected individuals than in healthy individuals. The risk of death due to cirrhosis among HBV-infected individuals is nine times that of non-HBV infected individuals. The risk of death due to HCC among HBV-infected individuals is more than 100 times that of non-HBV infected individuals. Overall, it is estimated that 15-25% of patients infected with chronic HBV will die prematurely due to various liver complications. The likelihood of death depends on the severity of liver disease and effectiveness of therapy. Several factors influence disease severity, including older age, necroinflammation and fibrosis stage at
histology, ongoing HBV replication, and CD4 depletion.\textsuperscript{22,28,29} As a patient’s immunodeficiency progresses, disease and response to therapy worsen.\textsuperscript{30}

HBV treatment is suppressive rather than curative. HBV treatment objectives include alanine aminotransferase normalization, improvement in liver histology and sustained suppression of serum HBV DNA.\textsuperscript{30-34} Successful treatment lowers liver inflammation, reverses liver fibrosis and reduces the risk for future hepatic decompensation or liver-related death.\textsuperscript{35} To maintain its benefit, treatment must be provided for long periods, often indefinitely.\textsuperscript{36}

Chronic HBV is determined by the presence of HBsAg or HBV DNA. HBsAg is a marker of HBV infection, appearing in serum 1-10 weeks after exposure to HBV (figure 2.2).\textsuperscript{37} In acute infections HBsAg becomes undetectable after 4-6 months.\textsuperscript{38} Chronic infection is defined as the persistence of HBsAg for more than 6 months. Current immunoassays are very sensitive, so it is rare that during infection HBsAg levels are undetectable.\textsuperscript{39} The presence of anti-HBs indicates recovery from HBV and provides lifelong immunity.\textsuperscript{38} Anti-HBs is produced early in the course of infection; however, it is not routinely detected until HBsAg clears. Very rarely, there is a short window period during which neither HBsAg nor anti-HBs are detectable. Less rare (~10-25% of the time) is the situation where HBsAg positive individuals have anti-HBs detected at the same time. This occurs most commonly in chronically infected patients\textsuperscript{40} with low level antibodies directed against a different subtype of HBsAg than that present in HBV infected patients.

HBeAg is a marker of HBV replication and infectivity, and is detectable a short time after the appearance of HBsAg (figure 2.2).\textsuperscript{38} HBeAg is associated with detectable HBV DNA replication and acute liver disease.\textsuperscript{38,41} Anti-HBe seroconversion occurs just before
anti-HBs seroconversion\textsuperscript{37} and is associated with the disappearance of HBV DNA and the resolution of liver disease.\textsuperscript{38} Anti-HBe can persist for years after acute infection and for decades in chronically infected patients.\textsuperscript{38}

Anti-HBe appears within one month of HBsAg\textsuperscript{37} and is detectable throughout the course of HBV infection (figure 2.2).\textsuperscript{38} It is the only marker of infection during the rare window period between the depletion of HBsAg and the appearance of anti-HBs.\textsuperscript{42} Anti-HBc is predominantly immunoglobulin M (IgM) class during acute infection; however, during recovery IgM anti-HBc declines while the titer of immunoglobulin G (IgG) anti-HBc rises. Therefore, detection of IgM anti-HBc is usually interpreted as an indication of acute HBV infection. On the other hand, approximately 20\% of patients have detectable anti-HBc for up to two years after the acute phase of infection. This, combined with the fact that IgM anti-HBc can be detected in chronically infected patients during HBV exacerbation, misdiagnosis of acute infection might occur for patients who are not previously known to have chronic infection.\textsuperscript{43} IgG anti-HBc persists in patients who recover from acute infection and in those who progress to chronic infection.\textsuperscript{38}

**HIV and Hepatitis B Co-infection**

HBV is more prevalent in HIV-infected individuals than in HIV-uninfected individuals. Worldwide, an estimated 2-4 million people are HIV/HBV co-infected\textsuperscript{44}, equating to 5-10\% of all HIV-infected individuals. In the general US population the prevalence of HBV is less than one percent.\textsuperscript{45} However, in HIV-infected populations the prevalence is higher, ranging from 6\% to 14\%.\textsuperscript{2,5,46-48} The prevalence of chronic HBV infection among HBV-unvaccinated HIV-infected individuals in HIV care is approximately
7.6%, suggesting that at least 60,000 individuals in the US are HIV/HBV co-infected and enrolled in HIV care.\(^\text{48}\)

HIV’s and HBV’s mutual mode of transmission is a key reason that HBV is more prevalent in HIV-infected individuals compared to HIV-uninfected individuals.\(^\text{49}\) HBV may be acquired prior to, concurrent with or subsequent to HIV infection. Both IVDU and MSM are the main risk factors for HIV/HBV co-infection. Other risk factors include gender (HIV/HBV co-infection is more common in males than in females)\(^\text{45,50}\), age (young adults are at the highest risk of HBV and HIV infection)\(^\text{50,51}\) and having multiple sexual partners.\(^\text{44,51}\) Another reason HBV is more prevalent in HIV-infected individuals compared to HIV-uninfected individuals is that a higher proportion (10-40%) of HIV-infected adults who acquire HBV will progress from acute to chronic infection\(^\text{52-56}\) compared to HIV-uninfected individuals (<10%).\(^\text{57,58}\)

The prevalence of HIV/HBV co-infection varies geographically, primarily due to differences in the principal route of transmission.\(^\text{36,59}\) In highly endemic areas vertical, or perinatal, transmission dominates.\(^\text{60}\) In low endemic regions such as the US, transmission is predominantly horizontal.\(^\text{18,60}\)

In HIV/HBV co-infected individuals liver damage can be caused in several ways: 1). by the direct toxic effects of ART\(^\text{61-64}\); 2). by hepatotoxicity of ART causing treatment interruption, which allows for HBV reactivation; 3). by the rigorous immune reconstitution induced by ART, which aggravates HBV infection leading to liver deterioration\(^\text{2,61,65-67}\) and 4). by the direct effects of HBV in the absence of ART.

HIV/HBV co-infected individuals have a more complex and limited efficacy of anti-HBV treatment options compared to HBV-infected individuals.\(^\text{36}\) Seven drugs have been
approved for the treatment of chronic HBV, including pegylated interferon α-2a, adefovir, entecavir, telivudine (LdT), 3TC, FTC and TDF. Of these, pegylated interferon α-2a and LdT have activity only against HBV. 3TC, FTC and TDF have activity against both HBV and HIV. ART, particularly initial ART, typically contains at least one HBV active agent (3TC) and since the introduction of TDF, ART frequently contains two active agents (TDF and FTC or 3TC). The optimal treatment regimen has not been defined, particularly for patients with chronic HBV who do not yet require anti-HIV therapy, because of limited data, the overlapping drug activity of both viruses and the development of both HIV and HBV resistance.\textsuperscript{30,68-72}

Treating HIV/HBV co-infected patients must be balanced between the likelihood of response to anti-HBV therapy, the need to treat HIV, the prevention of drug resistance and minimizing the risk of drug-induced hepatotoxicity. The ideal time for initiating ART in HIV-infected patients remains debated,\textsuperscript{73,74} although recent studies suggest initiating early may provide clinical benefit.\textsuperscript{75} How to modify treatment approaches in the presence of HBV co-infection remains poorly studied. Currently the International AIDS Society recommends that for HIV/HBV co-infected patients, treatment for HIV should be considered at any CD4 cell count.\textsuperscript{75} The US Department of Health and Human Services recommends treating HBV with pegylated interferon-alpha when treatment for HIV is not desirable.\textsuperscript{76}

HIV has a deleterious effect on HBV outcomes. Studies conducted in the pre-ART era suggested that there was no negative effect of HIV on HBV outcomes.\textsuperscript{49,52,77-79} Another early study suggested that the progression to liver disease is actually decreased in the presence of HIV.\textsuperscript{80} However, more recent studies have shown that cirrhosis develops more quickly in HIV/HBV co-infected individuals than in HBV-infected individuals.\textsuperscript{28,81,82} Once cirrhosis
develops, hepatic decompensation and evolution to end stage liver disease is increased in HIV/HBV co-infected individuals compared to HBV-infected individuals.\textsuperscript{28,81,83} HIV/HBV co-infection also leads to an increase in the proportion of deaths due to liver-related disease\textsuperscript{2,47}, an increase in the rate of HBV infectivity\textsuperscript{49,81,84}, an increase in the rate of HBV reactivation\textsuperscript{7} and a higher rate of chronic hepatitis.\textsuperscript{52,77,85}

Co-infection with HCV, hepatitis D (HDV) or multiple HBV/HCV/HDV infection worsens outcomes. HCV and HDV are common co-infectors of patients with HIV/HBV co-infection. HDV can result in the most severe form of chronic viral hepatitis\textsuperscript{86} and co-infection with HIV accelerates progression of delta-associated liver disease.\textsuperscript{86,87} The prevalence of multiple viral hepatitis (HBV/HCV, HBV/HDV, HCV/HBV/HDV) in HIV-infected individuals is low (<3%); however, the prevalence is much higher than in the general population.\textsuperscript{88} HIV-infected patients dually infected with HBV and HCV have an accelerated progression to liver disease compared to HIV-infected patients\textsuperscript{89} and are more likely to develop hepatocellular carcinoma.\textsuperscript{90} Liver related mortality is also increased in this population compared to HIV-infected patients co-infected with HBV alone.\textsuperscript{91}

The impact of HBV on the progression of HIV remains debated. Several studies have found no impact of HBV co-infection on immunological and virological responses to ART.\textsuperscript{47,53,62,92-96} However, other studies have found an effect of HBV co-infection on CD4 cell count and HIV RNA viral load. In a study of out-patients with chronic HBV, a higher rate of virologic failure was seen after initiation of ART in HIV-infected individuals compared to non-HIV infected individuals\textsuperscript{97}, possibly due to the higher incidence of hepatitis resulting in a higher rate of HIV treatment interruption. Another study found that HIV/HBV co-infected individuals delayed CD4 cell count recovery at week four after initiating ART.
compared to HIV-infected individuals; however, this effect was no longer present at week 48.

Research has found an increased risk of all-cause mortality among HIV/HBV co-infected individuals. At the same time, many studies have found no association. All of these studies occurred after the ART era began in 1997. Only a few studies have been reported in the United States, three of which were limited to homosexual men and another that was limited to veterans. The remaining two studies were performed in HIV clinics; however, both studies were small. Bonocini et al. looked at HBV-related and HIV-related deaths and concluded that while co-infection with HBV increased liver-related mortality, it had no effect on HIV-related mortality. Scharschmidt et al. found a significant effect of HBV on all-cause mortality. This large effect could not be explained by liver-related deaths alone. Determining the causes of death amongst this important population is a topic deserving more attention.

Summary

In summary, the widespread use of ART has substantially decreased HIV-related morbidity and mortality, and non-AIDS events, including liver-related complications are of increasing concern to HIV clinical care. Identifying HIV-infected patients who are at risk of HBV co-infection is important in order to target screening and prevention measures. Until the cohort of children who began routinely receiving HBV vaccine ages up, vaccinating high-risk individuals remains clinically relevant for patient management and essential for the improvement of HIV care. Therefore, in this project we identified predictors of HIV/HBV co-infection.
It is unclear whether HIV/HBV co-infected individuals have inferior outcomes compared to HIV mono-infected individuals. As such, we assessed the effect of HBV co-infection on all-cause mortality. Further, optimal treatment regimens for HIV/HBV co-infected patients remain debated. Answering this question is necessary to inform the care and management of HIV/HBV co-infected patients. Consequently, we also examined whether, and to what extent, TDF affects response to initial ART, specifically HIV virologic and immunologic responses.
FIGURE 2.1. Incidence of acute hepatitis B virus, United States

Source: http://www.cdc.gov/hepatitis/HBV/HBVfaq.htm#overview
FIGURE 2.2. Serologic pattern of hepatitis B virus

Source: Specter *Viral Hepatitis* 1999
CHAPTER THREE: DESCRIPTION OF DATA SOURCE

For this project we relied on available data from the CNICS. CNICS is a collaboration of observational clinical cohorts.

The CNICS study collects electronic medical records from eight sites across the United States (figure 3.1). Patients in the CNICS project are aged 18 years or older and initiated primary care at CNICS sites after January 1, 1995. The CNICS cohort population is diverse with respect to geographic distribution, age, sex, race/ethnicity and HIV transmission risk factor (table 3.1). As of September 2008 nearly 20% of patients in the combined cohort are female. Thirty-five percent are Black, 11% are Hispanic and 49% are White. The majority of patients are between the age of 30 and 49 (63%). MSM is the risk factor of greatest prevalence (46%), followed by heterosexual contact (20%) and combined MSM-IVDU (13%).

Approximately 1,400 new patients are added to the CNICS data each year and 10% leave care annually. The median follow-up time is 33 months. The majority of patients have been under care during the ART era.

Data, which are subject to rigorous standards for site data quality prior to data transmission, are uploaded directly from CNICS site electronic medical record (EMR) systems and are checked for adherence to the established standards for terminology, format, data verification and quality assurance. Site data quality control includes procedures specific for each data type: 1). Laboratory data are uploaded directly from Clinical Laboratory
Systems, and surveillance for coding changes and outliers is conducted; 2). Diagnoses are recorded prospectively in the EMR by the treating clinician and verified through systematic review of clinician progress notes and other medical records, event driven audits, and verification of random samples of events; 3). Medication data are entered by clinicians or prescription fill/refill data are uploaded directly from institutional pharmacy dispensing systems and verified through record review; 4). Each CNICS site maintains a death registry and queries the US Social Security Administration database and/or the National Death Index to confirm mortality data at least annually.\textsuperscript{102,103} In addition to querying administrative death registries, CNICS sites also employ active surveillance for deaths. The Data Management Core group oversees the quality assurance process.

We included all patients enrolled in one of the eight CFARs that feed data into CNICS who met the inclusion criteria. Our inclusion criteria were:

1. Documentation of HIV infection. (Only HIV-infected individuals are enrolled.)
2. At least 18 years of age.
3. Results from at least one HBsAg or HBV DNA test.
4. Initiated ART with no prior exposure to antiretroviral therapy.

All CNICS participants provide written informed consent. Our study was approved by the University of North Carolina at Chapel Hill Institutional Review Board. All analyses were conducted in SAS\textsuperscript{®} (version 9.1.3, SAS Institute, Inc., Cary, NC).
### TABLE 3.1. Distribution of 15,792 patients included in the Centers for AIDS Research Network of Integrated Clinical Systems, as of September 2008

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Site</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case Western Reserve University</td>
<td>1524</td>
<td>(9.7)</td>
</tr>
<tr>
<td>Fenway Community Health Center of Harvard University</td>
<td>1380</td>
<td>(8.7)</td>
</tr>
<tr>
<td>University of Alabama, Birmingham</td>
<td>2315</td>
<td>(14.7)</td>
</tr>
<tr>
<td>University of California, San Diego</td>
<td>3151</td>
<td>(20.0)</td>
</tr>
<tr>
<td>University of California, San Francisco</td>
<td>2390</td>
<td>(15.1)</td>
</tr>
<tr>
<td>University of Washington</td>
<td>2497</td>
<td>(15.8)</td>
</tr>
<tr>
<td>Johns Hopkins University</td>
<td>2535</td>
<td>(16.1)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 18</td>
<td>15</td>
<td>(0.1)</td>
</tr>
<tr>
<td>18-19</td>
<td>68</td>
<td>(0.4)</td>
</tr>
<tr>
<td>20-29</td>
<td>2350</td>
<td>(14.9)</td>
</tr>
<tr>
<td>30-39</td>
<td>6525</td>
<td>(41.3)</td>
</tr>
<tr>
<td>40-49</td>
<td>5073</td>
<td>(32.1)</td>
</tr>
<tr>
<td>50-59</td>
<td>1495</td>
<td>(9.5)</td>
</tr>
<tr>
<td>60-69</td>
<td>225</td>
<td>(1.4)</td>
</tr>
<tr>
<td>=70</td>
<td>41</td>
<td>(0.3)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>2907</td>
<td>(18.4)</td>
</tr>
<tr>
<td>Male</td>
<td>12883</td>
<td>(81.6)</td>
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<tr>
<td><strong>Race/Ethnicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>5456</td>
<td>(34.5)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1711</td>
<td>(10.8)</td>
</tr>
<tr>
<td>White</td>
<td>7794</td>
<td>(49.4)</td>
</tr>
<tr>
<td>Other</td>
<td>831</td>
<td>(5.3)</td>
</tr>
<tr>
<td><strong>HIV Risk Factor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSM*</td>
<td>7310</td>
<td>(46.3)</td>
</tr>
<tr>
<td>IVDU*</td>
<td>1018</td>
<td>(6.4)</td>
</tr>
<tr>
<td>MSM-IVDU</td>
<td>1993</td>
<td>(12.6)</td>
</tr>
<tr>
<td>Other</td>
<td>366</td>
<td>(2.3)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1934</td>
<td>(12.2)</td>
</tr>
</tbody>
</table>

* MSM=men who have sex with men; IVDU=intravenous drug user

Note: This table does not include the University of North Carolina, Chapel Hill.

Source: http://www.uab.edu/cnics/
FIGURE 3.1. Centers for AIDS Research Network of Integrated Clinical Systems sites

Source: http://www.uab.edu/cnics/cnics-sites
CHAPTER FOUR: METHODS

Specific Aim 1

Among ART-naïve HIV-infected individuals, assess the impact of HBV co-infection on time to mortality.

a. Compare demographic and clinical characteristics by HBV co-infection status.

b. Determine differences in time to mortality by HBV co-infection status stratified by calendar interval of therapy initiation.

Study Design Overview

To determine the impact of HBV on time to mortality among HIV-infected individuals we conducted a retrospective cohort study using data collected as part of the CNICS cohort study. The CNICS cohort study is an optimal population within which to study HIV/HBV co-infection as it is one of the largest HIV cohorts available and includes patients who have risk factors for HBV co-infection. The CNICS cohort also includes patients who initiated ART before and after modern therapy with efficacy against both HIV and HBV became available. We hypothesized that HBV co-infection was associated with a greater risk of death, but that this risk decreased over calendar time with the introduction of more potent HIV and HBV therapy. Our study was ruled as exempt by the UNC Institutional Review Board.
Study Population

The study population included patients enrolled in the CNICS cohort study who initiated ART between 01 January 1998 and 30 June 2008. CNICS captures comprehensive longitudinal demographic and clinical data from eight HIV treatment centers in the US. The CNICS study and data collection procedures have been previously described.\textsuperscript{104}

Inclusion Criteria

Our study included all consenting antiretroviral-naïve HIV-infected persons who presented to one of the eight HIV treatment centers included in CNICS. Additional inclusion criteria were that the patient had to be at least 18 years of age, had to initiate ART with at least three antiretroviral agents [one of which could not be a nucleoside(tide) reverse transcriptase inhibitor (NRTI)] between 01 January 1998 and 30 June 2008, and had to have at least one HBsAg or HBV DNA result prior to ART initiation to be included.

Data Management

Sample size: The sample size was fixed so we calculated the power available to detect a clinically relevant hazard ratio. We expected a minimum of 5,000 HIV-infected treatment naïve patients initiating ART who had at least one HBsAg or HBV DNA serology result. We assumed an HBV prevalence of 10\% and a two-sided alpha of 0.05. We varied the proportion of the cohort who died from 3\% to 15\% (figure 4.1).\textsuperscript{105,106} Under these conditions, with an expected mortality rate of 6\% during follow-up, the power to detect a hazard ratio of 1.3 or greater was over 80\%.
Approach to missing data: All patients in the CNICS cohort had data available to measure against our study inclusion criteria except 279 (6%) patients who did not have any HBsAg or HBV DNA results prior to ART initiation. Of the 4,427 patients who had available data and met the inclusion criteria for specific aim #1, 374 (9%) did not have any HCV antibody results. All other covariables had complete data. Because our data were largely complete, we performed a complete case analysis where we excluded patients who had missing information for HCV.

Measurements and Analysis Plan – Specific Aim 1a

Specific Aim 1a: Compare demographic and clinical characteristics by HBV co-infection status among ART-naïve HIV-infected individuals.

Measurements

Outcome: HBV co-infection was defined as a positive HBsAg or HBV DNA result prior to beginning ART.

Additional covariables: Additional patient data included demographic and clinical characteristics.

- Age at therapy initiation was calculated as the number of years between patients’ date of birth and date of ART start. For frequencies by calendar interval and HBV status, age was a continuous variable presented as median and interquartile range (IQR). For additional analyses, age was categorized into a dichotomous variable (≤40 years, > 40 years).

- Sex and MSM combined patients’ sex at birth and MSM status into a three-level categorical variable (male MSM, male non-MSM and female).
- Race/ethnicity was categorized into a dichotomous variable (white, non-white).
- History of IVDU was a dichotomous variable (yes, no).
- Type of initial ART was categorized into protease inhibitor (PI), ritonavir-boosted PI (PI/r), non-nucleoside reverse-transcriptase inhibitor (NNRTI) and Other, based on the ART regimen backbone agent.
- Presence of an AIDS defining clinical condition at time of ART initiation was a dichotomous variable (yes, no).
- HCV co-infection at time of ART initiation was a dichotomous variable (yes, no), based on whether the patient had a positive HCV antibody result.
- APRI score is a non-invasive method for assessing liver fibrosis.\textsuperscript{107-109} It was calculated using Wai’s formula: \((\text{AST/upper limit of normal considered as 40 IU/L})/\text{platelet count (expressed as platelets x } 10^9/\text{L}) \times 100\).\textsuperscript{110}
- CD4 cell count (cells/mm\(^3\)) was a continuous measure presented as median and IQR by calendar interval and HBV status. For additional analyses, CD4 cell count was categorized into a dichotomous variable based on distribution and association with the factor of interest.
- HIV RNA level (log\textsubscript{10} copies/mL) was a continuous measure presented as median and IQR by calendar interval and HBV status, and categorized as appropriate based on distribution and association with the factor of interest. For all analyses we considered an HIV RNA <400 copies/mL as undetectable since viral load assays varied over time and sites. As needed undetectable values were assigned one-half the limit of detection (i.e., 200 copies/mL) for analyses.
- Creatinine level (mg/dL) was a continuous measure presented as median and IQR by calendar interval and HBV status, and categorized as needed and appropriate.

- CNICS site is a categorical variable (Case Western Reserve University; Fenway Community Health Center of Harvard University; University of Alabama, Birmingham; University of California, San Diego; University of California, San Francisco; University of Washington; Johns Hopkins University; University of North Carolina, Chapel Hill).

**Data Analysis**

**Descriptive analysis:** We presented the number and percent of patients overall and stratified by HBV co-infection status as appropriate. We also presented the number and percent of patients overall and stratified by the calendar interval in which the patient initiated ART. Demographic and clinical characteristics were compared between patients with HIV/HBV co-infection and those with HIV mono-infection using Pearson’s chi-square test for categorical variables, Student’s t-test for normally distributed continuous variables and Wilcoxon’s rank sum test for non-normally distributed continuous variables.\textsuperscript{111} Covariables were compared between the three calendar intervals during which patients began ART using standard bivariable tests. All tests for assessing statistical significance were two-sided with $\alpha=0.05$.

**Predictive analysis:** Independent associations of having HBV co-infection were assessed using multivariable log-linear binomial regression. Risk ratios and 95% confidence intervals were calculated for each factor of interest. The equation for the log-linear binomial model can be expressed as:

$$\ln(P(D)) = \alpha + \beta_1X_1 + \beta_2X_2 + \cdots + \beta_nX_n$$
where $D$ is the outcome of interest and $X_1 \ldots X_n$ are the potential predictors. The interpretation of $e^{\beta_i}$ for the log-linear binomial model is the risk ratio comparing those with $X_i=1$ to those with $X_i=0$ (referent), holding all other covariables constant.

We first examined the individual bivariable relationships between each variable and the outcome. Covariables were included in the full model if the p-value from the corresponding bivariable analysis was less than 0.2. We then used backwards elimination, removing covariables from the model in order of p-value magnitude, to arrive at the final predictive model based on a p-value of less than 0.05.

**Measurements and Analysis Plan – Specific Aim 1b**

**Specific Aim 1b:** Among ART-naïve HIV-infected individuals, determine differences in time to mortality by HBV co-infection status stratified by calendar interval of therapy initiation.

**Measurements**

**Outcome:** Time to all-cause mortality was calculated as the number of days between patients’ ART start date and their date of death.

**Exposure:** HBV co-infection was defined as a positive HBsAg or HBV DNA result prior to beginning ART.

**Additional covariables:** Additional patient data included demographic and clinical characteristics as for specific aim 1a, except for age, CD4 cell count, $\log_{10}$ HIV RNA level and creatinine level at the time of ART initiation. These continuous variables were coded using splines with four equal knots based on the case distribution.\textsuperscript{112}
Data Analysis

Follow-up time was calculated as the number of days between ART initiation and the first of death from any cause, administrative censoring (at the first of two years following ART initiation or December 31, 2008), or attrition. Attrition was defined as the absence of a CD4 cell count or HIV RNA measure for more than 18 months (with the censor date equal to 18 months after the last available result). We employed an intention to continue treatment approach where patients were assumed to have remained on their initial ART for the duration of follow-up.

The Kaplan-Meier method and log-rank test were used to assess time to mortality by HBV co-infection status for the entire study period and for patients initiating ART during each of the calendar time intervals. Multivariable models were fit using Cox proportional hazards regression, which is based on the number of events per interval of time and models the hazard rate. While comparable to incidence rates, hazard rates are conditional on “survival” in the immediately preceding time interval. The proportional hazards model is expressed as:

\[ H(t_{ij}) = H_0(t_{ij})e^{\beta X_{ni} + \beta_2 X_{nij} + \cdots + \beta_n X_{niij}} \]

Where \( X=X_1, X_2, \ldots X_n \) is a vector of explanatory variables, \( H_0(t_{ij}) \) is the baseline hazard when \( X=0 \) and \( H(t_{ij}) \) is the hazard when \( X=x \). When \( X_i \) is a binary predictor variable, the interpretation of \( e^{\beta_i} \) is the hazard ratio comparing those with \( X_i=1 \) to those with \( X_i=0 \) (referent) at all times \( t \), adjusted for all other explanatory variables in the model.

An assumption of the proportional hazards model is that the hazard ratio in the model is assumed to be constant, or proportional, across time.\(^{113}\) We evaluated the proportional hazards assumption using likelihood ratio test results comparing models with and without a
time interaction term and by examining plots of the log of the cumulative hazards by time. If necessary, the proportional hazards assumption was relaxed by adding categorical or continuous time interactions. Goodness of fit was assessed using deviance residuals and influence statistics. 95% confidence limits were used as a measure of precision.

We evaluated effect measure modification (EMM) and confounding for HBV co-infection. We then constructed a single, fully adjusted model with the main exposure and all relevant interaction terms and confounders.

**Assessment of Effect Measure Modification:** We identified effect measure modifiers by considering the exposure-outcome relationship at each level of a third variable (the potential effect measure modifier) by including a product interaction term between the exposure and the potential effect measure modifier.\(^{114}\) EMM was examined only for variables for which stratified estimate would be qualitatively meaningful. We used a p-value of \(\alpha=0.10\) from the likelihood ratio test to indicate heterogeneity in the stratum-specific measures of association.\(^{115}\) Covariables found to be important effect measure modifiers were included in the multivariable model through an interaction term with the main exposure variable.

**Assessment of Confounding:** Potential confounders were identified through the existing literature and directed acyclic graph analysis (figure 4.2).\(^{116,117}\) Covariables that were not found to be effect measure modifiers and that led to a change in the unadjusted effect estimate by more than 10% according to the formula

\[
\ln \left| \frac{\text{unadjusted effect estimate}}{\text{adjusted effect estimate}} \right|
\]

were considered confounders and were included in the multivariable model.\(^{118}\)
Specific Aim 2

Among ART-naïve HIV/HBV co-infected individuals, assess response to ART by TDF receipt.

a. Compare demographic and clinical characteristics by TDF receipt.

b. Evaluate HIV virologic response to ART by TDF status.

c. Evaluate HIV immunologic response to ART by TDF status.

Study Population

The study population was a subset of the study population in specific aim 1, including those patients who were HIV/HBV co-infected at ART initiation.

Inclusion Criteria

The inclusion criteria were the same as for specific aim 1 with the addition of requiring a positive HBsAg or HBV DNA result prior to therapy initiation.

Data Management

Sample size: The sample size was fixed so we calculated the power available to detect a clinically relevant hazard ratio. As for specific aim 1, we expected a minimum of 5,000 HIV-infected treatment naïve patients initiating ART who had at least one HBsAg or HBV DNA serology result. We assumed an HBV prevalence of 10% and a two-sided alpha of 0.05. We varied the expected proportion of the cohort with virologic failure from 10% to 30% (figure 4.3)\textsuperscript{105,106} Under these conditions, with an expected event rate of 20% during follow-up, the power to detect a hazard ratio of 1.4 or greater was over 80%.
**Approach to missing data:** Of the 226 patients who met the inclusion criteria for specific aim #2, six (3%) did not have data for assessing liver function and an additional eight (4%) did not have any HCV antibody results. All other covariates had complete data. Because our data were largely complete, we performed a complete case analysis where we excluded patients who had missing information for liver function or HCV.

**Measurements and Analysis Plan – Specific Aim 2a**

**Specific Aim 2a:** Among ART-naïve HIV/HBV co-infected individuals, compare demographic and clinical characteristics by TDF receipt.

**Measurements**

**Outcome:** Inclusion of TDF in initial ART.

**Additional covariates:** Additional patient data included demographic and clinical characteristics as for specific aim 1a.

**Data Analysis**

**Descriptive analysis:** We presented the number and percent of patients overall and in each covariate category stratified by TDF status. As for specific aim 1a, covariates were compared between patients who did and did not receive TDF using Pearson’s chi-square test to compare proportions of categorical variables, Student’s t-test to compare normally distributed continuous variables and Wilcoxon’s rank sum test to compare non-normally distributed continuous variables.\textsuperscript{111} All tests for assessing statistical significance were two-sided with $\alpha=0.05$. 
Predictive analysis: Independent predictors of TDF use were assessed using multivariable log-linear binomial regression as described for specific aim 1a.

Measurements and Analysis Plan – Specific Aim 2b

Specific Aim 2b: Among ART-naïve HIV/HBV co-infected individuals, evaluate HIV virologic response to ART by TDF status.

Measurements

Outcome: Time to HIV virologic failure was defined as time to the first of two successive HIV RNA values >400 copies/mL after 16-weeks of ART exposure.¹¹⁹,¹²⁰

Exposure: Inclusion of TDF in initial ART, either alone or in combination with 3TC or FTC.

Additional covariables: Additional patient data included demographic and clinical characteristics as for specific aim 1b.

Data Analysis

Analyses were the same as for specific aim 1b with two exceptions. First, follow-up time started at 16-weeks post ART initiation. In order to give patients an opportunity to respond to initial ART, patients were not eligible to experience the virologic failure outcome until after this 16-week interval. Second, where the proportional hazards assumption was not met, the time following ART initiation was stratified at the point where the curves from the log of the cumulative hazards plot were no longer parallel. We confirmed the cut point by visually examining the plot of hazard ratios over time and by verifying the proportional
hazards assumption was met on both sides of the cut point. All analyses were then performed for time included on either side of the cut point.

**Measurements and Analysis Plan – Specific Aim 2c**

**Specific Aim 2c:** Among ART-naïve HIV/HBV co-infected individuals, evaluate HIV immunologic response to ART by TDF status.

**Measurements**

**Outcome:** CD4 cell count response.

**Exposure:** Inclusion of TDF in initial ART, either alone or in combination with 3TC or FTC.

**Additional covariables:** Additional patient data included demographic and clinical characteristics as for specific aim 1b.

**Data Analysis**

CD4 cell counts were measured at 6-monthly intervals following ART initiation. We employed an intention to treat approach where patients were assumed to have remained on their initial ART for the duration of follow-up.

We used multivariable linear regression fit with generalized estimating equations to estimate the association between TDF use and CD4 count response. We used an independent correlation structure and robust standard errors to account for repeat CD4 count measures. The linear regression model is expressed as:

\[ P(D) = \alpha + \beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_n X_n \]
where $D$ is the outcome of interest (CD4 count) and $X_1 \ldots X_n$ are the potential predictors. The interpretation of $\beta_i$ for the linear model is the average difference in CD4 count across time comparing those with $X_i=1$ to those with $X_i=0$ (referent), holding all other covariables constant.

EMM and confounding (figure 4.4) were evaluated as for specific aim 1b.
FIGURE 4.1. Power curves for specific aim 1 varying the proportion of the cohort who died between 3% and 15%
FIGURE 4.2. Directed acyclic graph showing the relationship between HBV co-infection and time to all-cause mortality for specific aim #1
FIGURE 4.3. Power estimates for specific aim 2 varying the proportion of the cohort with virologic failure between 10% and 30%
FIGURE 4.4. Directed acyclic graph showing the relationship between tenofovir disoproxil fumarate status and HIV virologic failure for specific aim #2

Unmeasured

Demographic characteristics:
- Age
- Sex
- Race
- HIV risk factor
- CNICS site

Clinical characteristics at therapy initiation:
- CD4 count
- HIV RNA level
- AIDS defining clinical condition
- HCV co-infection
- Liver function
- Kidney function

Treatment characteristics:
- Year of therapy initiation
- Type of initial therapy

Tenofovir disoproxil fumarate

Time to HIV virologic failure
CHAPTER FIVE: RECENT IMPROVEMENTS IN SHORT-TERM MORTALITY AMONG HIV AND HBV CO-INFECTED PATIENTS, 1998-2008 CNICS COHORT STUDY

Introduction

As antiretroviral therapy (ART) has reduced mortality from HIV, the proportion of deaths with liver-related causes has risen.\textsuperscript{122,123} HIV and hepatitis B virus (HBV) co-infected patients are more likely than HBV-uninfected patients to experience liver-related mortality, with HBV co-infection possibly accounting for some of the increase in the proportion of deaths with liver-related causes among HIV-infected individuals.\textsuperscript{47}

Tenofovir (TDF), emtricitabine (FTC) and lamivudine (3TC) are antiretroviral (ARV) agents with activity against both HIV and HBV. Combination TDF with either FTC or 3TC is effective for controlling HBV DNA among HIV-infected patients.\textsuperscript{124,125} TDF was approved for use in 2001, and by 2006, US treatment guidelines recommended TDF and 3TC/FTC as preferred agents for treating co-infected patients.\textsuperscript{126} At present, these drugs are not widely used in resource limited settings where HBV is more prevalent and HIV/HBV co-infection more common than in the US.\textsuperscript{127}

The relationship between HBV co-infection and mortality has not been evaluated in patients treated with antiretroviral therapy since the introduction of antiviral agents that have activity against both HIV and HBV. In this study, we assessed the effect of HBV co-infection on all-cause mortality among HIV-infected patients from 1998 to 2008 in a large multisite clinical cohort in the United States, the Centers for AIDS Research Network of
Integrated Clinical Systems (CNICS). We hypothesized that HBV co-infection is associated with a greater risk of death, but that this risk decreased with the introduction of more potent HIV and HBV therapy.

**Methods**

**Study population**

The study population included patients enrolled in CNICS, a large multisite HIV clinical cohort study in the US. CNICS captures comprehensive longitudinal demographic and clinical data from eight HIV treatment centers. The CNICS study and data collection procedures have been previously described.\(^{104}\) For these analyses we included all antiretroviral-naïve patients who initiated ART with at least three antiretroviral agents [one of which could not be a nucleoside(tide) reverse transcriptase inhibitor (NRTI)] between January 1, 1998 and June 30, 2008. Patients also had to have at least one hepatitis B surface antigen (HBsAg) or HBV DNA result prior to ART initiation to be included (n=98 were excluded because an HBV result was not available pre-ART initiation). Each CNICS site receives local Institutional Review Board approval, and this study was approved by the University of North Carolina at Chapel Hill Institutional Review Board.

**Measures**

HBV co-infection was defined as a positive HBsAg or HBV DNA result prior to beginning ART. Mortality included deaths from any cause and was determined by local CNICS site death searches as well as regular queries to the US Social Security Death Index.
Calendar time was divided into three time intervals to align with the introduction and uptake of TDF and FTC: 1998-2001; 2002-2004; and 2005-2008.

Patient demographic characteristics considered as affecting the relationship between HIV/HBV co-infection and mortality were age, sex, race/ethnicity, HIV risk transmission group [including men who have sex with men (MSM) and intravenous drug use (IVDU)] and CNICS site. Clinical factors were measured at ART initiation and included year of ART initiation, initial ART regimen anchor drug [non-nucleoside reverse-transcriptase inhibitor (NNRTI), protease inhibitor (PI) or ritonavir-boosted PI], AIDS defining clinical condition, hepatitis C virus (HCV) co-infection status, HIV RNA level, CD4 cell count and creatinine level.

Statistical Analysis

Follow-up time started at ART initiation and ended at the first of death from any cause, administrative censoring (at the first of two years following ART initiation or December 31, 2008), or attrition. We administratively censored follow-up at two years following ART initiation to ensure adequate sample size for making inferences in both groups of patients (HBV-infected and HBV-uninfected). Attrition was defined as the absence of a CD4 cell count or HIV RNA measure for more than 18 months (with the censor date equal to 18 months after the last available result). Clinical and demographic characteristics were compared across calendar time intervals and by HBV co-infection status with Pearson’s chi-square test, Student’s t-test, Wilcoxon’s rank sum test and one-way analysis of variance, as appropriate. Factors associated with HBV co-infection at ART initiation were assessed using multivariable log-linear binomial regression. For all analyses we used an intention to treat
approach where patients were assumed to have remained on their initial ART for the duration of follow-up.

The Kaplan-Meier method and log-rank test were used to assess time to mortality by HBV co-infection status for the entire study period and for patients initiating ART during each of the calendar time intervals. Multivariable models were fit using Cox proportional hazards regression. The proportional hazards assumption was assessed using likelihood ratio test results comparing models with and without a time interaction term and by examining plots of the log of the cumulative hazards by time. Confounders were selected based on the existing literature, use of causal diagrams and change-in-estimate calculations.\textsuperscript{117,118} All tests for assessing statistical significance were 2-sided with $\alpha=0.05$. All analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC).

**Results**

**Study Population**

Of the 3,706 patients included in this study 21% were women, 48% were White, 40% were Black and 12% were of other races/ethnicities. Patients’ median age at therapy initiation was 39 years (interquartile range [IQR]: 33, 45). The median year of ART initiation was 2004 (IQR: 2001, 2006). Eighteen percent of patients had a history of IVDU and 53% were MSM (66% of all men). The first ART included an NNRTI (56%), PI (21%), ritonavir-boosted PI (22%) and other agents (<1%). At ART initiation 28% of patients had an AIDS defining clinical condition and 15% were HCV co-infected. The median pre-ART CD4 cell count and HIV RNA levels were 176 cells/mm$^3$ (IQR: 47, 293) and 4.93 \text{log}_{10} \text{copies/mL}.
IQR: 4.44, 5.46) respectively. The median creatinine level was 0.90 mg/dL (IQR: 0.80, 1.00).

The number of patients initiating ART in each of the three calendar periods, 1998-2001, 2002-2004 and 2005-2008, was 954 (26%), 1,063 (29%) and 1,689 (46%) respectively. Differences across calendar time were seen for several patient characteristics (Table 1). Sex and MSM varied slightly across calendar time ($P <0.001$). The proportion of patients with a history of IVDU decreased over the study period from 23% to 16% ($P <0.001$). Ritonavir-boosted PIs were used most frequently during 2002-2004 and non-boosted PIs were used less frequently in more recent calendar years ($P <0.001$). The proportion of patients with HCV co-infection decreased from 20% to 13% ($P <0.001$). The median CD4 cell count at the time of ART initiation increased while the proportion of patients with an AIDS defining clinical condition decreased (both $P <0.001$). The median HIV RNA level decreased from 5.00 log$_{10}$ copies/ml (IQR: 4.47, 5.55) to 4.88 log$_{10}$ copies/ml (IQR: 4.35, 5.37) ($P=0.001$). No differences were seen across the three calendar periods for age, race/ethnicity, or creatinine level.

**Hepatitis B Co-infection**

Overall, 6% (n=212) of patients were HBV-infected at ART initiation, with prevalence stable from 1998-2008. HBV-infected patients were comparable to HBV-uninfected patients by most patient demographic and clinical characteristics at ART initiation (Table 2). However, HBV-infected patients were more likely to be men, both MSM and non-MSM ($P <0.001$), and to have a PI or NNRTI included in first ART ($P=0.034$). In multivariable analyses each of these factors remained associated with HBV infection (Table A.1).
Specifically, MSM and non-MSM men were over four and three times as likely to be HBV-infected in comparison to women, respectively (Relative Risk [RR]=4.41, 95% Confidence Interval [CI]: 2.44, 7.96; and RR=3.26 95% CI: 1.77, 6.01 respectively). Patients whose first ART included ritonavir-boosted PI were less likely to be HBV-infected compared to those receiving either an NNRTI or a PI (RR=0.59, 95% CI: 0.41, 0.86).

**Antiretroviral Therapy Provision**

The overall distribution of anchor drugs included in initial ART was generally similar for HBV-infected and HBV-uninfected patients across calendar years, with the exception noted above that HIV/HBV co-infected patients were more likely to receive an NNRTI or PI across all years (Figure 1). After the introduction of NNRTIs and ritonavir-boosted PIs, the proportion of patients receiving each was generally stable across time, while the proportion of patients receiving a PI decreased over time.

Among HIV/HBV co-infected patients initial therapy included TDF with FTC (n=106 ; 50%), TDF with 3TC (n=23; 11%), TDF alone (n=2; 1%), 3TC alone (n=77; 36%), and FTC alone in a single patient (<1%). Three HBV-infected patients did not receive TDF, FTC or 3TC as part of their first ART regimen. Among HBV-uninfected patients 1,449 (41%) received TDF with FTC, 296 (8%) received TDF with 3TC, 24 (1%) received TDF alone, 1,567 (45%) received 3TC alone, and 27 (1%) received FTC alone. The remaining 121 HBV-uninfected patients did not receive TDF, FTC or 3TC as part of their first ART regimen. Among the 2,120 patients, with and without HBV co-infection, who began therapy after 2003, 78% had TDF with FTC or 3TC included in their initial therapy. This proportion increased to 84% among the 1,265 patients who began therapy after 2005.
Hepatitis B Co-infection Effect on Mortality

Among the 3,706 patients in the study, 296 (8%) died during the two years of follow-up from ART initiation. The proportion of HBV uninfected patients who died decreased slightly during the latest calendar interval of therapy initiation, with 5, 5 and 3% of patients beginning ART in 1998-2001, 2002-2004 and 2005-2008 dying within two years, respectively (Supplemental figure 1). This decrease was not statistically significant (log-rank p-value comparing 1998-2001 vs. 2005-2008 = 0.175). In contrast, the proportion of HBV infected patients who died decreased four-fold over the calendar intervals of therapy initiation. Among HBV co-infected patients who initiated ART during 1998-2001, 2002-2004 and 2005-2008, 12, 10 and 3% died, respectively (log-rank p-value comparing 1998-2001 vs. 2005-2008 = 0.057).

Over the course of the study period, the difference in time to mortality comparing HBV-infected to uninfected patients diminished. During the 1998-2001 calendar interval of therapy initiation, HBV-infected patients had more than twice the hazard of death during their first two years on ART compared to HBV-uninfected patients (unadjusted HR=2.33, 95% CI: 1.00, 5.45) (Table 3, Figure 2). This result was consistent after adjusting for confounders (adjusted HR=2.20, 95% CI: 0.92, 5.23). In later calendar intervals the hazard ratio decreased to 2.00 (95% CI: 0.85, 4.63) for patients initiating therapy during 2002-2004 and to 0.95 (95% CI: 0.30, 3.05) for patients initiating therapy during 2005-2008. Further, adjusting for confounders did not appreciably change the estimates or their associated precision (adjusted HR=2.09, 95% CI: 0.86, 5.07 for patients initiating ART in 2002-2004; adjusted HR=0.96, 95% CI: 0.29, 3.16 for patients initiating ART in 2005-2008).
Discussion

In this large national HIV clinical cohort we observed a consistent proportion of HIV-infected patients initiating ART between 1998 and 2008 with HBV-infection at 6%. As expected, HBV-infected patients were more likely to be MSM\textsuperscript{44,48} and to have non-invasive testing consistent with fibrosis.\textsuperscript{128} In more recent calendar years patients were starting ART at higher CD4 cell counts and lower HIV RNA levels which has been documented by others.\textsuperscript{129} We observed reductions in short-term mortality following ART initiation in the most recent calendar years, consistent with other recent reports.\textsuperscript{130} We also observed a rapid uptake of new ARV agents as they became available.

Our most notable result was a substantial decrease in more recent calendar years of early mortality following ART initiation among HBV-infected patients. HBV-infected patients who began ART between 1998 and 2001 were over twice as likely to die in the first two years following therapy initiation compared to HBV-uninfected patients, but this difference disappeared in more recent calendar years, with no difference in time to death by HBV infection status among patients starting ART between 2005 and 2008. These findings suggest that during the first two years following ART initiation, HBV-infection may no longer increase the risk of all-cause death among HIV-infected individuals.

The reduction in early mortality among HBV-infected patients remained after adjustment for patient demographic and clinical characteristics at ART initiation, including sex and MSM, IVDU, type of initial ART, AIDS defining clinical condition, HCV infection, CD4 cell count, and HIV RNA level. These results suggest that the changes in mortality are not explained by changes in the patient population across calendar time intervals. A possible
reason for the decrease was the rapid and widespread uptake of combination TDF with 3TC or FTC as part of initial ART. Unfortunately, we were unable to assess the extent to which these anti-HBV agents affected the reductions in mortality directly. Because nearly all HBV-infected patients received TDF (with 3TC or FTC) as soon as it became available, resulting in lack of heterogeneity across calendar time, we were unable to make desirable comparisons.

Others have shown that, among HIV/HBV co-infected individuals, provision of anti-HBV agents including TDF with 3TC or FTC reduces HBV DNA levels and ongoing liver damage. Additionally, early reports suggest that HIV RNA levels may also be lower among HIV/HBV co-infected individuals treated with ART including TDF and 3TC or FTC than without these anti-HBV agents. Therefore it is likely that the use of these anti-HIV and HBV agents as part of ART reduces early mortality among HIV/HBV co-infected patients; however, whether this is the effect of better treatment of HBV, HIV or some combination thereof requires further study.

Our results from the pre-2002 calendar years are consistent with those from studies that evaluated mortality among HIV/HBV co-infected patients during the late 1990s and early 2000s. HIV/HBV co-infected patients included in the EuroSIDA study between 1997 and 2004 were 50% more likely to die from all causes and over 200% more likely to die from liver-related causes compared to HBV-uninfected patients. HIV/HBV co-infected patients enrolled in the Multicenter AIDS Cohort Study who initiated therapy between 1996 and 2006 were also at a higher risk of death compared to HBV-uninfected patients. To the best of our knowledge, our results are the first to isolate the effect of HIV/HBV co-infection on time to mortality following the widespread use of TDF with FTC or 3TC.
Our study has a number of strengths including generalizability to patients receiving clinical care in the United States. The CNICS clinical cohort is one of the largest clinical cohort studies and has a national distribution of study sites with a diverse patient population and demographic composition that is largely consistent with national figures. We were also able to include patients initiating ART over a long period of time spanning 1998 through 2008, and captured the rapid uptake of ARVs efficacious for treatment of both HIV and HBV.

However our study also has a number of limitations. We assessed all-cause mortality in these analyses and were unable to specifically consider liver-related mortality. Given the small sample size of HBV co-infected patients even in this large cohort, we were limited to assessing mortality over the first two years following ART initiation. Additional work on mortality by HBV status over longer follow-up time is needed. We were unable to account for time from HIV infection, but we did adjust for CD4 cell count as an indicator of HIV disease progression at ART initiation. We were also unable to account for time from HBV infection. As with all observational studies our results may also be affected by residual unmeasured confounding.

Additional work is indicated that considers response to agents with activity against both HIV and HBV (TDF, FTC and 3TC), including HBV DNA and HIV RNA suppression, immunologic response, liver disease progression, other liver and non-liver related incident morbidity and mortality, especially over longer periods of time. Though our results suggest that short term mortality is comparable by HBV status among patients receiving modern ART, it is unclear whether this is sustainable over the lifespan of co-infected patients,
particularly in the presence of resistance evolution.\textsuperscript{136-138} Therefore, ongoing efforts to identify other agents with activity against both HIV and HBV are indicated.

Further, effective treatment is not a substitute for prevention. Despite the HBV vaccine being available in the US for nearly 30 years, a substantial proportion of high-risk individuals have not been immunized.\textsuperscript{139} Because HBV infection can occur before, after or concurrent with HIV infection, and because HBV vaccine-induced immunity is compromised in HIV-infected patients\textsuperscript{140}, it is vital that efforts continue to achieve wide-spread uptake of HBV vaccination through routine and other immunization opportunities.\textsuperscript{141,142}

The association between HBV infection and decreased time to mortality among HIV-infected patients who began ART early in our study period disappeared for patients initiating ART in more recent calendar years. Because uptake of TDF with 3TC or FTC was rapid, it was not possible to measure the extent to which modern ART may have been responsible for the attenuated risk of HBV on time to all-cause mortality; however, we ruled out the contribution of several competing explanations. Our findings have implications for clinical care in the US and for strategies to best improve treatment for patients in resource limited settings where the burden of HIV/HBV co-infection is high.
**TABLE 5.1.** Patient characteristics by calendar period of antiretroviral therapy initiation among 3706 HIV-infected patients, CFAR Network of Integrated Clinical Systems 1998-2008

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>954</td>
<td>1063</td>
<td>1689</td>
<td></td>
</tr>
<tr>
<td>Age in years, median (IQR)</td>
<td>38 (33, 44)</td>
<td>39 (33, 45)</td>
<td>39 (32, 46)</td>
<td>0.120</td>
</tr>
<tr>
<td>White race/ethnicity</td>
<td>429 (45)</td>
<td>503 (47)</td>
<td>835 (49)</td>
<td>0.084</td>
</tr>
<tr>
<td>Sex and MSM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male MSM</td>
<td>465 (49)</td>
<td>559 (53)</td>
<td>931 (48)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male non-MSM</td>
<td>293 (31)</td>
<td>257 (24)</td>
<td>441 (26)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>196 (21)</td>
<td>247 (23)</td>
<td>317 (19)</td>
<td></td>
</tr>
<tr>
<td>IVDU</td>
<td>215 (23)</td>
<td>180 (17)</td>
<td>263 (16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Type of initial ART</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI</td>
<td>327 (34)</td>
<td>167 (16)</td>
<td>278 (16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PI/r</td>
<td>85 (9)</td>
<td>329 (31)</td>
<td>422 (25)</td>
<td></td>
</tr>
<tr>
<td>NNRTI</td>
<td>532 (56)</td>
<td>563 (53)</td>
<td>985 (58)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>10 (1)</td>
<td>4 (&lt;1)</td>
<td>4 (&lt;1)</td>
<td></td>
</tr>
<tr>
<td>AIDS defining clinical condition</td>
<td>311 (33)</td>
<td>347 (33)</td>
<td>385 (23)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HBV co-infection</td>
<td>52 (5)</td>
<td>62 (6)</td>
<td>98 (6)</td>
<td>0.917</td>
</tr>
<tr>
<td>HCV co-infection</td>
<td>187 (20)</td>
<td>157 (15)</td>
<td>226 (13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CD4 cell count (cells/mm$^3$), median (IQR)</td>
<td>130 (29, 294)</td>
<td>156 (39, 268)</td>
<td>211 (74, 303)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HIV RNA level (log$_{10}$ copies/ml), median (IQR)</td>
<td>5.00 (4.47, 5.55)</td>
<td>4.98 (4.55, 5.50)</td>
<td>4.88 (4.35, 5.37)</td>
<td>0.001</td>
</tr>
<tr>
<td>Creatinine level (mg/dL), median (IQR)</td>
<td>0.90 (0.70, 1.00)</td>
<td>0.90 (0.80, 1.00)</td>
<td>0.90 (0.80, 1.09)</td>
<td>0.248</td>
</tr>
</tbody>
</table>

**NOTES:** IQR=inter-quartile range; MSM=men who have sex with men; IVDU=intravenous drug use; ART=antiretroviral therapy; PI=protease inhibitor, PI/r=ritonavir-boosted protease inhibitor; NNRTI=non-nucleoside reverse-transcriptase inhibitor; Other=other antiretroviral agents including fusion and integrase inhibitors; HBV=hepatitis B virus; HCV=hepatitis C virus
TABLE 5.2. Patient characteristics by hepatitis B co-infection at antiretroviral therapy initiation among 3706 HIV-infected patients, CFAR Network of Integrated Clinical Systems 1998-2008

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HBV-uninfected N (%)</th>
<th>HBV-infected N (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>3494</td>
<td>212</td>
<td></td>
</tr>
<tr>
<td>Age in years, median (IQR)</td>
<td>39 (33, 45)</td>
<td>39 (33, 44)</td>
<td>0.759</td>
</tr>
<tr>
<td>White race/ethnicity</td>
<td>1669 (52)</td>
<td>98 (46)</td>
<td>0.663</td>
</tr>
<tr>
<td>Sex and MSM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male MSM</td>
<td>1814 (52)</td>
<td>141 (67)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male non-MSM</td>
<td>932 (27)</td>
<td>59 (28)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>748 (21)</td>
<td>12 (6)</td>
<td></td>
</tr>
<tr>
<td>IVDU</td>
<td>625 (18)</td>
<td>33 (16)</td>
<td>0.390</td>
</tr>
<tr>
<td>Year of ART initiation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005-2008</td>
<td>1591 (46)</td>
<td>98 (46)</td>
<td>0.917</td>
</tr>
<tr>
<td>2002-2004</td>
<td>1001 (29)</td>
<td>62 (29)</td>
<td></td>
</tr>
<tr>
<td>1998-2001</td>
<td>902 (26)</td>
<td>52 (24)</td>
<td></td>
</tr>
<tr>
<td>Type of initial ART</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI</td>
<td>721 (21)</td>
<td>51 (24)</td>
<td>0.034</td>
</tr>
<tr>
<td>PI/r</td>
<td>804 (23)</td>
<td>32 (15)</td>
<td></td>
</tr>
<tr>
<td>NNRTI</td>
<td>1951 (56)</td>
<td>129 (61)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>18 (1)</td>
<td>0 (0.00)</td>
<td></td>
</tr>
<tr>
<td>AIDS defining clinical condition</td>
<td>972 (28)</td>
<td>71 (33)</td>
<td>0.075</td>
</tr>
<tr>
<td>HCV co-infection</td>
<td>541 (15)</td>
<td>29 (14)</td>
<td>0.480</td>
</tr>
<tr>
<td>CD4 cell count (cells/mm³), median (IQR)</td>
<td>179 (49, 293)</td>
<td>128 (33, 294)</td>
<td>0.101</td>
</tr>
<tr>
<td>HIV RNA level (log₁₀ copies/ml), median (IQR)</td>
<td>4.93 (4.45, 5.46)</td>
<td>4.89 (4.38, 5.34)</td>
<td>0.194</td>
</tr>
<tr>
<td>Creatinine level (mg/dL, median (IQR))</td>
<td>0.90 (0.80, 1.00)</td>
<td>0.90 (0.80, 1.00)</td>
<td>0.821</td>
</tr>
</tbody>
</table>

NOTES: IQR=inter-quartile range; MSM=men who have sex with men; IVDU=intravenous drug use; ART=antiretroviral therapy; PI=protease inhibitor, PI/r=ritonavir-boosted protease inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; Other=other antiretroviral agents including fusion and integrase inhibitors; HCV=hepatitis C virus
**TABLE 5.3.** Effect of hepatitis B co-infection at antiretroviral therapy initiation on time to mortality stratified by year of therapy initiation among 3706 HIV patients, CFAR Network of Integrated Clinical Systems 1998-2008

<table>
<thead>
<tr>
<th>Year of ART initiation</th>
<th>Hepatitis B</th>
<th>Yes</th>
<th>No</th>
<th>HR (95% CI) [P-value]</th>
<th>Unadjusted</th>
<th>Adjusted†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998-2001</td>
<td>Yes</td>
<td>2.33 (1.00, 5.45)</td>
<td>0.051</td>
<td>2.39 (1.00, 5.70)</td>
<td>0.051</td>
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</tr>
<tr>
<td></td>
<td>No</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>2002-2004</td>
<td>Yes</td>
<td>2.00 (0.85, 4.63)</td>
<td>0.110</td>
<td>2.25 (0.94, 5.38)</td>
<td>0.069</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>2005-2008</td>
<td>Yes</td>
<td>0.95 (0.30, 3.05)</td>
<td>0.935</td>
<td>1.00 (0.31, 3.27)</td>
<td>0.999</td>
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<tr>
<td></td>
<td>No</td>
<td>1</td>
<td>1</td>
<td></td>
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</tr>
</tbody>
</table>

† Models adjusted for age, race/ethnicity, sex, HIV exposure, initial antiretroviral therapy, AIDS defining clinical condition, hepatitis C co-infection, pre-therapy CD4 count, pre-therapy HIV RNA level, pre-therapy creatinine level and CNICS site.

NOTES: Models fit with Cox proportional hazards regression; HR=hazard ratio; CI=confidence interval; ART=antiretroviral therapy
FIGURE 5.1. Initial antiretroviral therapy across calendar time among 3706 HIV-infected patients, CFAR Network of Integrated Clinical Systems 1998-2008

HBV-uninfected (N=3494)  
- PI  
- NNRTI  
- PI/r  
- Other

HBV-infected (N=212)  
- PI  
- NNRTI  
- PI/r  
- Other

Proportion of patients  
Year of antiretroviral therapy initiation

1998-2001
Log-rank p = 0.044

2002-2004
Log-rank p = 0.104

2005-2008
Log-rank p = 0.934

Time from antiretroviral therapy initiation (months)
**SUPPLEMENTAL TABLE 5.1.** Patient characteristics by calendar period of antiretroviral therapy initiation and hepatitis B co-infection status among 3706 HIV-infected patients, CFAR Network of Integrated Clinical Systems 1998-2008

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HBV-uninfected</th>
<th></th>
<th></th>
<th>N (%)</th>
<th>N (%)</th>
<th>N (%)</th>
<th>P</th>
<th>HBV-infected</th>
<th></th>
<th></th>
<th>N (%)</th>
<th>N (%)</th>
<th>N (%)</th>
<th>P</th>
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<tbody>
<tr>
<td>Total</td>
<td>902</td>
<td>1001</td>
<td>1591</td>
<td></td>
<td></td>
<td></td>
<td>0.174</td>
<td>52</td>
<td>62</td>
<td>98</td>
<td></td>
<td></td>
<td>0.417</td>
<td></td>
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<td>Age in years, median (IQR)</td>
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<td>White race/ethnicity</td>
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<td>0.084</td>
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<tr>
<td>Sex and MSM</td>
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<td></td>
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<td>0.001</td>
<td>0.001</td>
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</tr>
<tr>
<td>Male MSM</td>
<td>434 (48)</td>
<td>516 (52)</td>
<td>864 (54)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>31 (60)</td>
<td>43 (69)</td>
<td>67 (68)</td>
<td></td>
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</tr>
<tr>
<td>Male non-MSM</td>
<td>274 (30)</td>
<td>241 (24)</td>
<td>417 (26)</td>
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<td></td>
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<td></td>
<td>19 (37)</td>
<td>16 (26)</td>
<td>24 (24)</td>
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<tr>
<td>Female</td>
<td>194 (22)</td>
<td>244 (24)</td>
<td>310 (19)</td>
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<td></td>
<td>2 (4)</td>
<td>3 (5)</td>
<td>7 (7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV RNA level (log_{10} copies/ml), median (IQR)</td>
<td>5.00 (4.47, 5.56)</td>
<td>5.00 (4.58, 5.51)</td>
<td>4.88 (4.35, 5.38)</td>
<td>&lt;0.001</td>
<td>5.00 (4.47, 5.46)</td>
<td>4.87 (4.38, 5.23)</td>
<td>4.81 (4.37, 5.24)</td>
<td>0.613</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>CD4 cell count (cells/mm³), median (IQR)</td>
<td>132 (29, 294)</td>
<td>157 (39, 267)</td>
<td>214 (78, 303)</td>
<td>&lt;0.001</td>
<td>95 (27, 276)</td>
<td>133 (46, 290)</td>
<td>143 (33, 307)</td>
<td>0.527</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine level (mg/dL), median (IQR)</td>
<td>0.90 (0.70, 1.00)</td>
<td>0.90 (0.80, 1.00)</td>
<td>0.90 (0.80, 1.08)</td>
<td>0.252</td>
<td>0.80 (0.75, 0.90)</td>
<td>0.90 (0.80, 1.00)</td>
<td>0.97 (0.80, 1.09)</td>
<td>0.830</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**NOTES:** IQR=inter-quartile range; MSM=men who have sex with men; IVDU=intravenous drug use; ART=antiretroviral therapy; PI=protease inhibitor, PI/r=ritonavir-boosted protease inhibitor; NNRTI=non-nucleoside revers-transcriptase inhibitor; Other=other antiretroviral agents including fusion and integrase inhibitors; HBV=hepatitis B virus; HCV=hepatitis C virus
SUPPLEMENTAL FIGURE 5.1. Time from antiretroviral therapy initiation to mortality among 3494 HIV-infected patients and 212 HIV/HBV co-infected patients, stratified by year of therapy initiation, CFAR Network of Integrated Clinical Systems.

HIV mono-infected patients

Proportion of patients who died

1998-2001, N    902   889        879             861                  795
2002-2004, N   1001   984        954             954                 856
2005-2008, N   1591  1576       1027            1027                723

1998-2001, N    52      50          47               46                    42
2002-2004, N    62     59         58               57                   44
2005-2008, N    98     98         78               63                    41

Time from antiretroviral therapy initiation (months)

HEV co-infected patients

98-01 vs. 05-08 Log-rank p = 0.057
CHAPTER SIX: TENOFOVIR DISOPROXIL FUMARATE FOR TREATMENT OF HIV AND HEPATITIS B CO-INFECTED PATIENTS – EFFECT ON HIV OUTCOMES

Introduction

The widespread use of modern ART has substantially decreased HIV-related morbidity and mortality. However, non-AIDS events, including liver-related complications, are of increasing concern in HIV clinical care. The prevalence of HBV in the general US population is <1%. Among HIV-infected patients HBV prevalence is 6-14%, due largely to mutual modes of transmission and shared risk factors. Additionally, 10-40% of HIV-infected patients who acquire HBV progress from acute to chronic infection compared to <10% of HIV-uninfected individuals. Co-infection HBV can lead to substantial liver complications including cirrhosis and end stage liver disease. In one study of HBV-infected men with and without HIV coinfection, HIV/HBV co-infected patients were approximately 19-times more likely to die from liver disease compared to those with HBV infection alone. Based on these and other data, HBV has been recognized as a significant cause of morbidity and mortality in HIV-infected patients.

Three antiretroviral agents have activity against both HIV and HBV, 3TC, FTC and TDF. Current HIV treatment guidelines recommend that HIV/HBV co-infected individuals receive TDF with either 3TC or FTC, in addition to other agents. This recommendation is based on demonstrated TDF efficacy on HBV virologic response, HBV drug resistance, progression of HBV, renal safety and survival.
Among HIV/HBV co-infected patients TDF improves HBV-related outcomes, but thorough evaluation of HIV outcomes would also inform clinical decisions. Therefore we used a large and representative US clinical cohort study to examine whether, and to what extent, TDF affects response to initial ART, specifically HIV RNA suppression and CD4 count response.

Methods

Study Population

CNICS is a large HIV clinical cohort that includes 8 clinical sites across the US. CNICS collects comprehensive data on more than 20,000 HIV-infected adults who have received HIV care since 1995. For this study we included all antiretroviral-naïve patients who were HBV co-infected and initiated ART with at least three antiretroviral agents [one of which could not be a nucleoside(tide) reverse transcriptase inhibitor (NRTI)] between 1 January 1998 and 30 June 2008. The study was approved by the University of North Carolina at Chapel Hill Institutional Review Board.

Measures

Patients with positive HBsAg or HBV DNA results prior to ART initiation were considered HBV co-infected. The primary exposure was inclusion of TDF in initial ART, either alone or in combination with 3TC or FTC. HIV virologic failure was defined as having two successive HIV RNA values >400 copies/mL after 16-weeks of ART exposure, and the first date where HIV RNA was >400 copies/mL was used as the date of virologic
failure.\textsuperscript{119,120} Five patients whose last HIV RNA was >400 copies/mL with no confirmatory measure were considered to have virologic failure.

Patient demographic and clinical characteristics at ART initiation considered as affecting treatment responses were age, sex, race/ethnicity, HIV risk transmission group [including MSM and IVDU], year of ART initiation, initial ART regimen anchor drug [NNRTI, PI or PI/r], AIDS defining clinical condition, HCV co-infection status, APRI score, HIV RNA level, CD4 count, creatinine level and CNICS site. APRI score is a non-invasive method for assessing liver fibrosis.\textsuperscript{107-109} It was calculated using Wai’s formula: (AST/upper limit of normal considered as 40 IU/L)/platelet count (expressed as platelets $\times 10^9$/L) $\times 100$.\textsuperscript{110}

\textit{Statistical analysis}

For HIV virologic failure, follow-up time began at 16 weeks post-ART initiation. For CD4 count response, follow-up time began at ART initiation. Follow-up ended at the first of death from any cause, administrative censoring (December 31, 2008), or loss to follow-up. Loss to follow-up was defined as the absence of CD4 count or HIV RNA measures for more than 18 months (with the censor date equal to 18 months after the last available result). Clinical and demographic characteristics were contrasted by TDF use with Pearson’s chi-square test, Student’s t-test and Wilcoxon’s rank sum test, as appropriate. Independent predictors of TDF use were assessed using multivariable log-linear binomial regression.

Time to HIV virologic failure was evaluated among the 208 (98\%) patients under observation at 16 weeks post-ART initiation. Patients were eligible to experience the virologic failure outcome following this 16-week interval. Of four patients excluded because
they did not complete 16 weeks of ART, three did not receive TDF in initial ART and each died at 2, 6 and 11 weeks following ART initiation; one patient received TDF and died 6 weeks after initiating ART. All 212 patients were considered for CD4 count response. For all analyses we used an intention to treat approach where patients were assumed to have remained on their initial ART for the duration of follow-up.

The Kaplan-Meier method and log-rank test were used to evaluate time to virologic failure by TDF use. Multivariable models were fit using Cox proportional hazards regression. Likelihood ratio test results comparing models with and without a time interaction term, as well as plots of the log of the cumulative hazards by time were examined to assess the proportional hazards assumption. Where this assumption was not met, the time following ART initiation was stratified at the point where the curves from the log of the cumulative hazards plot were no longer parallel. We confirmed the cut point by visually examining the plot of hazard ratios over time and by verifying the proportional hazards assumption was met on both sides of the cut point. All analyses were then performed for time included on either side of the 19-month cut point.

Linear regression fit with generalized estimating equations was used to estimate the association between TDF use and CD4 count response. We used an independent correlation structure and robust standard errors to account for repeat CD4 count measures. Confounders were selected based on the existing literature, use of causal diagrams and change-in-estimate calculations. Continuous variables age, CD4 count, log10 HIV RNA level and creatinine level at the time of ART initiation were included in models using splines with four equal knots based on the case distribution. In all models we adjusted for CNICS site.
Because TDF was not available in all calendar years covered by these analyses and then prescribed widely to HBV co-infected patients, we performed three supplemental analyses. First, we repeated the analyses using calendar year of ART initiation as a proxy for the exposure. Second, we performed a sensitivity analysis using only data from 2002-2003. In these calendar years we observed some but not all patients with HBV infection receiving TDF. Third, we accounted for patients receiving zidovudine (AZT) or stavudine (D4T) in their initial ART regimen as discontinuation of ARV drugs known to have high toxicity levels can influence HIV outcomes. An additional sensitivity analysis was done for time to virologic failure where we assumed the five patients with no confirmatory HIV RNA measure $>400$ copies/mL did not fail. All tests for assessing statistical significance were 2-sided with $\alpha=0.05$. All analyses were performed using SAS® version 9.2 (SAS Institute Inc., Cary, NC).

**Results**

*Study Population*

Of the 212 HIV/HBV co-infected patients, 6% were female, 46% were White, 43% Black and 11% of other races/ethnicities. The median age at ART initiation was 39 years (IQR: 33, 44) and the median year of ART initiation was 2004 (IQR: 2002, 2006). Sixteen percent of patients had a history of IVDU and 67% of patients were MSM (71% of men). At ART initiation 33% of patients had experienced a previous AIDS defining clinical condition and 14% were HCV co-infected. The median pre-ART CD4 count, HIV RNA level and creatinine level were 128 cells/mm$^3$ (IQR: 33, 294), $4.89 \log_{10}$ copies/mL (IQR: 4.38, 5.34) and 0.9 mg/dL (IQR: 0.8, 1.0) respectively.
The 212 HIV/HBV co-infected patients were a subset of 3,706 HIV-infected patients who initiated ART meeting our inclusion criteria during the 11 years of this study and for whom (HBsAg) or HBV DNA results were available at ART initiation. HIV/HBV co-infected patients differed from the 3,494 HIV mono-infected patients with respect to sex, MSM, initial ART regimen anchor drug and APRI. HBV co-infected versus HIV mono-infected patients were 6% and 21% were women, 28% and 27% were non-MSM men, and 66% and 52% were MSM men, respectively (all $P < 0.001$). Compared to HIV mono-infected patients, HBV co-infected patients were less likely to receive a PI/r (15% versus 23%, $P=0.034$) and more likely to have an APRI indicating liver damage (56% versus 28%, $P < 0.001$). No meaningful differences were observed by age, race/ethnicity, IVDU, year of ART initiation, AIDS defining clinical condition, HCV co-infection status, pre-ART CD4 count, HIV RNA level, or creatinine level.

**Tenofovir Use**

Almost all HBV co-infected patients (n=209 of 212) received at least one anti-HBV agent as part of their initial ART; TDF alone (n=2, 1%), TDF with FTC or 3TC (n=129, 61%), or FTC or 3TC alone (n=78, 37%). TDF use increased sharply from 20% in 2002 to 50% in 2003 to > 90% for all subsequent study years. Among the 160 patients who began ART after 2001, 82% received TDF (Figure 6.1). The median year of ART initiation and follow-up time was 2001 (IQR: 2000, 2002) and 60 months (IQR: 26, 86) for patients without TDF, and 2006 (IQR: 2004, 2007) and 23 months (IQR: 16, 38) for patients with TDF (all $P <0.001$).
Factors associated with TDF use included no history of IVDU, no HCV co-infection at ART initiation, and ART initiation in more recent calendar years (Table 6.1). In multivariable analyses considering sex, MSM, history of IVDU, initial ART regimen anchor drug and HCV co-infection, no factors were independently predictive of TDF use (Table B.1). Repeating these analyses among patients who began ART in 2002 or 2003 yielded the same result.

_Tenofovir Effect on HIV RNA Response_

Among the 208 patients considered for analysis at 16 weeks post-ART initiation, 98, 86, 60 and 43% remained under study observation through 6, 12, 24 and 36 months post-ART initiation, respectively. At these 6-month intervals post-ART initiation the percent on ART was 86, 81, 77 and 82%, and the percent with suppressed HIV RNA levels was 68, 68, 61 and 49%, and 32, 32, 39 and 51% among patients who did and did not receive TDF, respectively.

The cumulative probability of HIV virologic failure by 6, 12, 24 and 36 months following ART initiation was 10, 20, 25 and 29%. Compared to patients who received TDF, patients who did not receive TDF were more likely to experience HIV virologic failure following ART initiation (unadjusted HR=1.72, 95% CI: 1.02, 2.87, adjusted HR=1.59, 95% CI: 0.91, 2.80) (Table 6.2, Figure 6.2). The proportional hazards assumption was not met for all time following ART initiation. Rather, the effect of TDF on HIV virologic failure varied across time, with a clear change in estimate at 19 months post-ART initiation. Between 16 weeks and 19 months following ART initiation, not receiving TDF conferred a greater risk of HIV virologic failure (HR=2.64, 95% CI: 1.45, 4.79). This result was consistent after
adjusting for confounders (adjusted HR=2.31, 95% CI: 1.20, 4.45). However, among patients who achieved and maintained HIV virologic suppression through 19 months of therapy (n=118), the use of TDF did not appreciably affect HIV virologic failure post-19 months of ART (unadjusted HR=0.44, 95% CI: 0.15, 1.31; adjusted HR=0.37, 95% CI: 0.09, 1.48). Considering the five patients with no confirmatory HIV RNA measures as not having failed virologically did not alter inferences.

The risk of HIV virologic failure was greater in earlier calendar years of ART initiation (Figure 6.3). The unadjusted HRs for years 1998-1999, 2000-2001 and 2002-2005 in comparison to 2006-2008 were 2.80 (95% CI: 1.23, 6.39), 2.23 (95% CI: 1.11, 4.47) and 1.35 (95% CI: 0.69, 2.63), respectively. The effect of TDF use on HIV virologic failure among patients starting ART in 2002-2003 (n=41) was consistent with those observed in our primary analyses, as was the effect of TDF use on HIV virologic failure adjusted for AZT and D4T use.

*Tenofovir Effect on CD4 Count Response*

The median CD4 count at ART initiation was 137 cells/mm$^3$ for the 131 patients with TDF use and 119 cells/mm$^3$ for the 81 patients without TDF use ($P=0.451$). Median CD4 counts increased for all patients following ART initiation; however, no significant differences were seen between patients with and without TDF use (Supplemental Figure 6.1A). After adjustment for ART initiation age, race/ethnicity, sex, MSM, IVDU, initial ART, AIDS defining clinical condition, HCV co-infection, APRI, CD4 count, HIV RNA level and creatinine level patients without TDF use had an average difference in CD4 across time from ART initiation of -22 cells/mm$^3$ (95% CI: -57, 13) compared to patients with TDF
use (Supplemental Table 6.1). Our findings did not change when we considered only the subset of patients who achieved and maintained HIV virologic suppression (n=164) (Supplemental Figure 6.1B).

**Discussion**

In this large US HIV clinical cohort we found that HIV/HBV co-infected patients who received TDF as part of their initial ART were more likely to achieve and maintain HIV RNA suppression over the first year and a half on therapy. Our findings support current US treatment guidelines which recommend treating HIV/HBV co-infected patients with combination regimens that include TDF. To date treatment recommendations were largely based on evidence of TDF activity against HBV. These findings suggest that TDF use may also lead to better HIV outcomes among HIV/HBV co-infected patients. Identifying the optimal therapeutic management of HIV/HBV co-infected patients is not only relevant to individuals living in the US, it is also increasingly relevant to areas of the world where HBV is endemic and modern ART is increasingly available.147,148

Among patients who achieved and maintained suppressed HIV RNA through the first year and a half on ART, TDF use did not appear to further affect the risk of HIV virologic failure. This is consistent with clinical and clinical trial observations that once virologic suppression is achieved virologic failure is uncommon, even with regimens that may not be considered optimal.120 However, it is possible that our inability to detect a difference after the first year and a half on ART could be due to calculating period-specific hazard ratios rather than cumulative measures. Period-specific hazard ratios do not account for possible selection bias caused by differential depletion over time of exposed and unexposed patients susceptible
to virologic failure. In addition, our ability to detect more subtle differences after sustained successful response to initial ART was restricted by available sample size and the limited number of HIV virologic failures observed. Consequently any conclusions about longer term effects of TDF use on HIV RNA response would require additional follow-up time in a larger cohort of patients. While we included many of the known predictors of HIV outcomes in our analyses, unmeasured confounders may lead to bias in our estimates.

The CNICS clinical cohort is one of the largest US cohort studies and has a national distribution of study sites, with a diverse patient population and demographic composition that is largely consistent with national figures. In this group of patients we observed a rapid uptake of TDF as it became available for clinical use in the US, with essentially all HBV co-infected patients receiving TDF with either 3TC or FTC after 2003. This rapid uptake of TDF use limited our ability to account for calendar year differences in assessing the effect of TDF use on HIV response; however, the improvement in HIV RNA responses across calendar years of ART initiation were striking and highly coincident with the uptake of TDF use. Therefore we repeated our analysis among patients who began ART in 2002 and 2003, during which time there was some heterogeneity in TDF use. These findings supported our primary results, although were imprecise due to the reduced sample size. Coincident to the rapid uptake of TDF among patients in our study was the discontinuation of other ARV drugs known to have high toxicity levels, in particular AZT and D4T. Therefore the better HIV virologic outcomes we observed for patients receiving TDF in initial ART may in part be due to less tolerable drugs being discontinued and/or replaced. In additional analyses we accounted for patients receiving AZT or D4T and although the effect of TDF on HIV response was somewhat lessened, our conclusions were unchanged.
Our results are consistent with a couple of smaller studies conducted to date. For example, two studies designed to evaluate the effect of TDF on HBV outcomes among HIV/HBV co-infected patients reported that patients who received TDF had superior HIV RNA response rates, but no differences were observed in CD4 count outcomes.\textsuperscript{125,133} We also did not find evidence that TDF use was associated with improved CD4 count responses; however, other large prospective randomized trials have observed a small rise in CD4 count with TDF/FTC and Efavirenz compared to other therapies.\textsuperscript{150} Furthermore, in this study we were unable to assess whether TDF use was associated with clinical HIV progression, as measured by either new AIDS defined clinical conditions or mortality, or with drug-related toxicity as measured by changes in renal function. Further longitudinal follow-up with a larger sample size would support these additional analyses, providing clinical endpoint evidence and strengthening evidence for guidelines in developed and developing regions.

Treatment for HIV/HBV co-infection is more complex than treatment for either HIV or HBV alone. It must balance multiple factors, such as the likelihood of response to anti-HBV therapy, the need to treat HIV, the prevention of drug resistance, minimizing the risk of drug-induced hepatotoxicity and managing rising liver transaminases when they occur. Additional issues complicating treatment for co-infected patients are the limited choice of anti-HBV drugs and that treatment for both infections is suppressive rather than curative, and therefore must be provided for long, often indefinite, periods.\textsuperscript{36} Data are limited whether TDF alone or in combination with 3TC/FTC is superior for improving HBV-related outcomes among HBV mono-infected patients and long-term HIV-related outcomes among HIV/HBV co-infected patients.\textsuperscript{124,151} We were unable to test for this difference as nearly everyone received TDF with either 3TC or FTC.
In summary, among HIV/HBV co-infected patients TDF use was associated with greater HIV RNA control early after ART initiation. Our study provides evidence that in addition to improving HBV outcomes, TDF use among HIV/HBV co-infected patients improves HIV outcomes. Our findings further support current US treatment guidelines and aid in identifying optimal therapy for HIV/HBV co-infected individuals who reside in developing settings.
### TABLE 6.1. Patient characteristics by tenofovir use at antiretroviral therapy initiation among HIV and hepatitis B co-infected patients, Center for AIDS Research Network of Integrated Clinical Systems 1998-2008

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Tenofovir</th>
<th>No Tenofovir</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>131 (62)</td>
<td>81 (38)</td>
<td></td>
</tr>
<tr>
<td><strong>Age in years, median (IQR)</strong></td>
<td>39 (32, 44)</td>
<td>39 (35, 43)</td>
<td>0.856</td>
</tr>
<tr>
<td><strong>White race/ethnicity</strong></td>
<td>62 (63)</td>
<td>36 (37)</td>
<td>0.682</td>
</tr>
<tr>
<td><strong>Sex and MSM</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male MSM</td>
<td>91 (65)</td>
<td>50 (35)</td>
<td>0.176</td>
</tr>
<tr>
<td>Male non-MSM</td>
<td>31 (53)</td>
<td>28 (47)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>9 (75)</td>
<td>3 (25)</td>
<td></td>
</tr>
<tr>
<td><strong>IVDU</strong></td>
<td>13 (39)</td>
<td>20 (61)</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>Year of ART initiation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005-2008</td>
<td>96 (98)</td>
<td>2 (2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>2002-2004</td>
<td>35 (56)</td>
<td>27 (44)</td>
<td></td>
</tr>
<tr>
<td>1998-2001</td>
<td>0 (0)</td>
<td>52 (100)</td>
<td></td>
</tr>
<tr>
<td><strong>Type of initial ART</strong>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI</td>
<td>26 (51)</td>
<td>25 (49)</td>
<td>0.130</td>
</tr>
<tr>
<td>PI/r</td>
<td>23 (72)</td>
<td>9 (28)</td>
<td></td>
</tr>
<tr>
<td>NNRTI</td>
<td>82 (64)</td>
<td>47 (36)</td>
<td></td>
</tr>
<tr>
<td><strong>AIDS defining clinical condition</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>42 (59)</td>
<td>29 (41)</td>
<td></td>
<td>0.575</td>
</tr>
<tr>
<td><strong>HCV co-infection</strong></td>
<td>9 (31)</td>
<td>20 (69)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>APRI &gt; 0.5</strong></td>
<td>70 (59)</td>
<td>49 (41)</td>
<td>0.314</td>
</tr>
<tr>
<td><strong>CD4 count (cells/mm³), median (IQR)</strong></td>
<td>137 (30, 297)</td>
<td>119 (35, 255)</td>
<td>0.451</td>
</tr>
<tr>
<td><strong>HIV RNA level (log₁₀ copies/ml), median (IQR)</strong></td>
<td>4.83 (4.38, 5.23)</td>
<td>4.92 (4.38, 5.47)</td>
<td>0.495</td>
</tr>
<tr>
<td><strong>Creatinine (mg/dL), median (IQR)</strong></td>
<td>1.00 (0.80, 1.10)</td>
<td>0.90 (0.80, 1.00)</td>
<td>0.158</td>
</tr>
</tbody>
</table>

**NOTES:** HBV=hepatitis B virus; IQR= interquartile range; MSM=men who have sex with men; IVDU=intravenous drug use; ART= antiretroviral therapy; PI=protease inhibitor, PI/r=ritonavir-boosted protease inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; HCV=hepatitis C virus; APRI=AST-platelet Ratio Index
**TABLE 6.2.** The effect of tenofovir use at antiretroviral therapy initiation on HIV virologic failure among 208 HIV and HBV co-infected patients, Center for AIDS Research Network of Integrated Clinical Systems 1998-2008

<table>
<thead>
<tr>
<th>Time from ART initiation*</th>
<th>All time</th>
<th>0-19‡ months</th>
<th>&gt; 19‡ months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unadjusted</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.72 (1.02, 2.87)</td>
<td>0.040</td>
<td>2.64 (1.45, 4.79)</td>
</tr>
<tr>
<td>Yes</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **Adjusted†**              |          |              |              |
| Tenofovir                  |          |              |              |
| No                        | 1.59 (0.91, 2.80) | 0.106 | 2.31 (1.20, 4.45) | 0.012 | 0.37 (0.09, 1.48) | 0.160 |
| Yes                       | 1        |              |              |

* Models fit with Cox proportional hazards regression
† Models adjusted for age, race/ethnicity, sex, HIV exposure, initial antiretroviral therapy, AIDS defining clinical condition, hepatitis C co-infection, pre-therapy AST-platelet Ratio Index, pre-therapy CD4, pre-therapy HIV viral load, pre-therapy creatinine level and CNICS site
‡ 19 months following ART initiation is the stratification point for which time on both sides satisfies the proportional hazards assumption
NOTES: ART= antiretroviral therapy; HR=hazard ratio; CI=confidence interval
FIGURE 6.1. HIV and HBV co-infected patients by year of antiretroviral therapy initiation and tenofovir use, Center for AIDS Research Network of Integrated Clinical Systems 1998-2008

<table>
<thead>
<tr>
<th>Calendar Year</th>
<th>Total</th>
<th>1998</th>
<th>1999</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>No tenofovir, n</td>
<td>81</td>
<td>7</td>
<td>10</td>
<td>19</td>
<td>16</td>
<td>16</td>
<td>11</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tenofovir, n</td>
<td>131</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>11</td>
<td>20</td>
<td>25</td>
<td>24</td>
<td>28</td>
<td>19</td>
</tr>
</tbody>
</table>
FIGURE 6.2. Time from antiretroviral therapy initiation to HIV virologic failure stratified by tenofovir use among 208 HIV and HBV co-infected patients, Center for AIDS Research Network of Integrated Clinical Systems 1998-2008

<table>
<thead>
<tr>
<th></th>
<th>No tenofovir</th>
<th>Tenofovir</th>
</tr>
</thead>
<tbody>
<tr>
<td>N total</td>
<td>78</td>
<td>130</td>
</tr>
<tr>
<td>N event (cumulative)</td>
<td>9</td>
<td>8</td>
</tr>
</tbody>
</table>

Log-rank p < 0.038
FIGURE 6.3. Time from antiretroviral therapy initiation to HIV virologic failure stratified by year of initiation among 208 HIV and HBV co-infected patients, Center for AIDS Research Network of Integrated Clinical Systems 1998-2008
**SUPPLEMENTAL TABLE 6.1.** The effect of tenofovir use on CD4 counts across time following antiretroviral therapy initiation among HIV and HBV co-infected patients, Center for AIDS Research Network of Integrated Clinical Systems 1998-2008

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=212)</th>
<th>HIV RNA suppressed patients (n=164)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Average difference in CD4 count (cells/mm$^3$) (95% CI) [P-value]</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Unadjusted</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir</td>
<td>No</td>
<td>-55 (-114, 3) 0.065</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td><strong>Adjusted for pre-therapy CD4 count</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir</td>
<td>No</td>
<td>-29 (-63, 5) 0.096</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td><strong>Fully adjusted†</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir</td>
<td>No</td>
<td>-22 (-57, 13) 0.215</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>1</td>
</tr>
</tbody>
</table>

* Models fit with linear regression fit with generalized estimating equations. An independent correlation structure and robust standard errors were used to account for repeat CD4 measures.
† Models adjusted for age, race/ethnicity, sex, HIV exposure, initial antiretroviral therapy, AIDS defining clinical condition, hepatitis C co-infection, pre-therapy AST-platelet Ratio Index, pre-therapy CD4, pre-therapy HIV RNA level, pre-therapy creatinine level and CNICS site.
SUPPLEMENTAL FIGURE 6.1. Box and whisker plots of CD4 counts at 6 month intervals following antiretroviral therapy initiation by tenofovir use among HIV and HBV co-infected patients, Center for AIDS Research Network of Integrated Clinical Systems 1998-2008: (A) all patients (n=212); and (B) patients who achieved and maintained HIV RNA suppression (n=164)
CHAPTER SEVEN: DISCUSSION

Summary of Findings

In this project we described several findings which bring new light to current published literature on HIV/HBV co-infection. In our first specific aim, we found a substantial decrease in more recent calendar years of early mortality following ART initiation among HIV/HBV co-infected patients. HBV-infected patients who began therapy between 1998 and 2001 were over twice as likely to die in the first two years following therapy initiation compared to HBV-uninfected patients, but this difference attenuated in more recent calendar years, with no difference in time to death by HBV infection status among patients starting ART between 2005 and 2008. These findings suggest that during the first two years following ART initiation, HBV co-infection may no longer increase the risk of all-cause mortality among HIV-infected individuals.

In our second specific aim, we found that HIV/HBV co-infected patients who received TDF as part of their initial ART were more likely to achieve and maintain HIV RNA suppression over the first year and a half on therapy. Among patients who achieved and maintained suppressed HIV RNA during this interval, TDF use did not appear to further affect the risk of HIV virologic failure. This is consistent with clinical and clinical trial observations that once virologic suppression is achieved virologic failure is uncommon, even with regimens that may not be considered optimal.\textsuperscript{120} However, our ability to detect more subtle differences after sustained successful response to initial ART was restricted by
available sample size and the limited number of HIV virologic failures observed. Consequently any conclusions about longer term effects of TDF use on HIV RNA response would require additional follow-up time in a larger cohort of patients.

These findings are reassuring, particularly since we observed no decrease in the prevalence of HBV co-infection across the study period. However, while we found that HBV co-infection does not contribute to liver-related mortality in the short-term, whether HBV co-infection accounts for some of the rise in liver-related mortality in the long-term remains unknown.

**Strengths and Limitations**

A major limitation of our analyses was rapid and widespread uptake of ARVs efficacious for treatment of both HIV and HBV, in particular TDF with FTC or 3TC. Even in this large cohort, the small number of HBV co-infected patients and the lack of heterogeneity in treatment over calendar time meant we could not measure the extent to which these anti-HBV agents were responsible for the decrease in early mortality and the improvement in HIV viral control separate from the collective improvements in the management of HIV patients between the late 1990s and late 2000s. However, we ruled out the contribution of several competing explanations, including changes in patient demographic and clinical characteristics over calendar time.

Our studies are, to date, the largest to explore HIV outcomes and mortality among HIV/HBV co-infected individuals. Also, our study population is largely representative of the HIV-infected population in the US, supporting the generalizability of our findings. Finally,
our studies are, to the best of our knowledge, the first to capture and document the rapid uptake of ARVs efficacious for treatment of both HIV and HBV.

Clinical and Public Health Significance

HBV has been recognized as a significant cause of morbidity and mortality in HIV-infected patients.\textsuperscript{2,47,145} An effective vaccine against HBV has been available in the US for nearly 30 years; however, a substantial proportion of high-risk individuals have not been immunized.\textsuperscript{139}

As we found in the CNICS cohort with the prevalence of HBV infection steady at 6% between 1998 and 2008, preventive efforts have not yet been successful at reducing HBV infection among HIV-infected individuals. For these reasons, effective HBV treatment remains a high priority for HIV care.

Treatment for HIV/HBV co-infection is more complex than treatment for either HIV or HBV alone. It must balance multiple factors, such as the likelihood of response to anti-HBV therapy, the need to treat HIV, the prevention of drug resistance, minimizing the risk of drug-induced hepatotoxicity and managing rising liver transaminases when they occur. Additional issues complicating treatment for co-infected patients are the limited choice of anti-HBV drugs and that treatment for both infections is suppressive rather than curative, and therefore must be provided for long, often indefinite, periods.\textsuperscript{36} Though a limitation for our analyses, it is important to recognize that timely and extensive uptake of improved treatment, as we observed in the CNICS cohort, has large clinical and public health benefits.

Our findings support current US treatment guidelines which recommend treating HIV/HBV co-infected patients with combination regimens that include agents efficacious for
both HIV and HBV, in particular TDF. To date treatment recommendations were largely based on evidence of TDF activity against HBV. These findings suggest that TDF use may also lead to better HIV outcomes and to improvements in short-term mortality among HIV/HBV co-infected patients.

In the US and other developed settings the prevalence of HBV is not high, even among HIV-infected individuals. But in resource limited settings, the story is different. Worldwide two billion people have been infected with HBV and nearly 400 million live with chronic infection. The geographic areas with the largest burden of HBV are the same as those with the largest burden of HIV, and given shared risk factors, co-infection is common. Therefore our findings have important implications for prioritizing treatment in these areas. They also provide evidence that increasing the utilization of agents efficacious for both HIV and HBV may substantially improve HIV-related outcomes and short-term mortality for a great number of people.

**Future Directions**

In the presence of resistance evolution ongoing efforts to identify new agents with activity against both HIV and HBV is necessary. Further, effective treatment is not a substitute for prevention. Since HBV infection can occur before, after or concurrent with HIV infection, and because HBV vaccine-induced immunity is compromised in HIV-infected patients, it is vital that efforts continue to achieve wide-spread uptake of HBV vaccination through routine and other immunization opportunities.

Additional work on mortality by HBV status is necessary to determine whether the improvement in mortality we observed during the first two years following therapy initiation
is sustained for longer periods. This will need to occur in a cohort with longer follow-up of patients who were treated with modern therapy efficacious for both HIV and HBV. Further, additional work is indicated that considers response to agents with activity against both HIV and HBV on HIV RNA suppression, immunologic response, liver disease progression and liver-related mortality. Longer longitudinal follow-up with a larger sample size would support these additional analyses, providing clinical endpoint evidence and strengthening evidence for guidelines in developed and developing regions.

Conclusions

Aging up of the cohort of infants who began receiving HBV vaccine as part of the routine childhood immunization schedule, together with expanding overall coverage of HBV vaccine will hopefully bring the end of HIV/HBV co-infection in the US. Unfortunately, this same outcome will not be seen in resource limited settings for quite some time. Therefore understanding the most efficacious treatment options for HIV/HBV co-infected individuals is necessary in order to enable the least advantaged patients to have the best health outcomes possible. Efforts to expand the use of agents with activity against both HIV and HBV are needed, as well as careful monitoring to ensure the positive benefits seen in our studies, as well as those for HBV-related outcomes, are also seen for HIV/HBV co-infected patients living in resource limited settings.
APPENDIX A. RESULT OF LOG-LINEAR BINOMIAL REGRESSION MODEL OF HBV CO-INFECTION

TABLE A.1. Patient characteristics associated with hepatitis B co-infection at antiretroviral therapy initiation among 3706 HIV-infected patients 1998-2008, CFAR Network of Integrated Clinical Systems

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Full model*</th>
<th>Final model*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR (95% CI)</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td></td>
<td>P-value</td>
<td>P-value</td>
</tr>
<tr>
<td>Sex and MSM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male MSM</td>
<td>4.46 (2.47, 8.05)</td>
<td>4.41 (2.44, 7.96)</td>
</tr>
<tr>
<td>Male non-MSM</td>
<td>3.22 (1.75, 5.94)</td>
<td>3.26 (1.77, 6.01)</td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Type of initial ART</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI</td>
<td>1.05 (0.77, 1.44)</td>
<td>1.07 (0.79, 1.46)</td>
</tr>
<tr>
<td>PI/r</td>
<td>0.57 (0.39, 0.83)</td>
<td>0.59 (0.41, 0.86)</td>
</tr>
<tr>
<td>NNRTI</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>AIDS defining clinical condition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.27 (0.97, 1.68)</td>
<td>1.07 (0.79, 1.46)</td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>APRI &gt; 0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.07 (2.36, 3.99)</td>
<td>3.12 (2.40, 4.05)</td>
</tr>
<tr>
<td>≤ 0.5</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

* Full and final models fit with multivariable log-linear binomial regression and include all characteristics listed in respective column plus site.

NOTES: RR=relative risk; 95% CI=95% confidence interval; MSM=men who have sex with men; ART=antiretroviral therapy; PI=protease inhibitor, PI/r=ritonavir-boosted protease inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; APRI=AST-to-platelet ratio index
APPENDIX B. RESULT OF LOG-LINEAR BINOMIAL REGRESSION MODEL OF TDF USE

TABLE B.1. Patient characteristics associated with tenofovir use at antiretroviral therapy initiation among 212 HIV/HBV co-infected patients 1998-2008, CFAR Network of Integrated Clinical Systems

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Full model* RR (95% CI)</th>
<th>P-value</th>
<th>Final model† RR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex and MSM</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male MSM</td>
<td>0.82 (0.47, 1.42)</td>
<td>0.475</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male non-MSM</td>
<td>0.83 (0.48, 1.43)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVDU</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.84 (0.56, 1.25)</td>
<td>0.389</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
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</tr>
<tr>
<td>Type of initial ART</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI</td>
<td>0.81 (0.62, 1.06)</td>
<td>0.122</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI/r</td>
<td>1.06 (0.82, 1.37)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NNRTI</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV co-infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.66 (0.41, 1.08)</td>
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</tr>
<tr>
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</tr>
</tbody>
</table>

* Full and final models fit with multivariable log-linear binomial regression and include all characteristics listed in respective column plus site.
† No covariables were independently associated with tenofovir use.
NOTES: RR=relative risk; 95% CI=95% confidence interval; MSM=men who have sex with men; IVDU=intravenous drug user; ART=antiretroviral therapy; PI=protease inhibitor, PI/r=ritonavir-boosted protease inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; HCV=hepatitis C virus
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