THE SYNDROMIC OF HEPATITIS CO-INFECTION AND SUBSTANCE USE AMONG PEOPLE LIVING WITH HIV: INSIGHTS FROM BALTIMORE AND BANGKOK

by
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Abstract

The research presented in this dissertation explores the impact of hepatitis B virus (HBV) and hepatitis C virus (HCV) coinfection on the health of those living with HIV, and emphasizes the role substance use plays in the care of those with HIV/HCV.

The first paper explores barriers to HCV care in the interferon era and compares those who initiated treatment for HCV to those who did not in the Johns Hopkins HIV Clinical Cohort. Non-black and those with advanced fibrosis were more likely to have initiated HCV treatment, while those who reported active drug use or missed a higher proportion of clinic visits were less likely to have initiated treatment.

The second paper explores the relationship between HBV and/or HCV co-infection on mortality of those with HIV in early (1996-2001) and later (2002-2013) antiretroviral treatment (ART) eras. We conducted a survival analysis comparing HIV, HIV/HBV, HIV/HCV, and HIV/HBV/HCV patients. In this analysis, later ART substantially reduced mortality among HIV mono-infected individuals but not among all groups of coinfected patients, even after adjustment for age, CD4 count, and levels of HIV RNA suppression. Tenofovir and pegylated interferon did not significantly impact all-cause or liver-related mortality for coinfected patients.

The third paper documents increasing incidence of HCV among a Bangkok-based cohort of men who have sex with men (MSM) who were diagnosed with acute HIV. Previously, MSM were not considered to be at high risk for HCV infection in Thailand, and no incident HCV
infections were identified between 2009-2014. However, since that time, HCV incidence has increased to 44.8 per 1000 PY in 2018. Methamphetamine use, group sex, and syphilis were associated with incident HCV.

Taken together, these papers highlight the impact of substance use on the likelihood that people living with HIV 1) acquire viral hepatitis and 2) receive treatment for co-infection. Additionally, it draws attention to persistently increased mortality rates among individuals co-infected with HIV and viral hepatitis despite the availability of treatment for HIV, HBV, and HCV. Interventions are needed to address factors underlying these disparities, and should focus on mitigating the effect of substance use disorder on engagement in clinical care.
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Preface

Mark Sulkowski has been my research and clinical mentor during my infectious diseases fellowship, dissertation, and in my early professional life. I will always appreciate his patience, honesty, wisdom, and support. He has had a tremendous impact on my personal and professional trajectory, and has helped provide me with opportunities that I would not have otherwise had at both at Johns Hopkins and in Thailand. I will always be thankful for his continued support of my non-traditional path.

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Chapter 1:
Introduction
Injecting drug use and infectious diseases risk

Since the beginning of the HIV epidemic, people who inject drugs (PWID) have been disproportionately infected by HIV(1). UNAIDS has defined them as a key population, meaning they are at increased risk of HIV acquisition secondary to injecting, irrespective of the epidemic type or local context(2). Sharing injecting equipment is one of the most efficient methods of transmission of bloodborne viruses including HIV, hepatitis B, and hepatitis C due to direct inoculation into the bloodstream(3). Injection-related health risks, including skin and soft tissue infections, sepsis, and endocarditis, are also causes of morbidity and mortality among PWID.

While HIV risk among PWID is often focused on injecting, syphilis rates have also been higher among PWID in many settings and associated with increased sexual risk behaviors related to drug use such as exchanging sex for drugs, sex work, or sex with other PWID(4, 5). For PWID, undiagnosed and untreated syphilis and other STIs can increase the risk of sexual acquisition and transmission of HIV with both other PWID as well as non-injecting populations(6).

Due to structural and societal issues including criminalization of injecting drug use, high rates of incarceration, limited access to evidence-based treatment and care for drug dependence, and stigma and discrimination, PWID often face obstacles in accessing comprehensive health-related interventions and care. Incarceration can often lead to unsafe injection practices due to lack of availability of sterile needles and syringes as well as little access to treatment for opioid or other drug use disorders(7). Sterile needle and syringe programs (NSPs), supervised injecting facilities, and medications for opioid use disorder in the
form of methadone or buprenorphine have been firmly established by public health programs to reduce drug-related harm, and can reduce HIV incidence. In addition, these interventions can reduce rates of death due to overdose(8, 9). Unfortunately, access to many of these programs remain limited. In the US, there was a longstanding ban on federal funding for NSPs until 2016. As local and state governments needed to fund or allow for needle exchange, there were geographic disparities in their availability(10). Government agencies and the public sector also do not support NSPs in Thailand, leading to very low coverage rates as community-based outreach workers are largely responsible for distribution of injection equipment. While the World Health Organization recommends 200 needles and syringes to be distributed per PWID annually, the average number of sterile needles a PWID in Thailand accessed through NSP was 12 in 2017(11).

Illicit drug use is largely criminalized globally. Therefore, prevalence and patterns of injecting drug use can change based on global and local production and supply chains for synthetic and organic precursors for drugs, trade and trafficking routes, and demand(12). In 2017, a global review reported the majority (82.9%) of PWID report opioids as their primary drug of choice(13). While heroin has been entrenched in some urban cities such as Baltimore for decades, there has been a national increase in heroin use over the past decade. This is largely attributed to aggressive pharmaceutical marketing leading to widespread prescription of opioids across the US, resulting in increased numbers of people addicted to opioids(14, 15). The opioid epidemic has driven a demographic shift in new injectors to young white people in rural communities, with subsequent increase in HIV and HCV incidence in these areas. In 2016, 215
people were infected with HIV in Scott County, Indiana, highlighting how lack of access to HIV testing and clean needles can fuel a local, PWID-driven disease outbreak (16).

In low and middle-income countries, both overdose and AIDS are primary causes of death for PWID (17), and in the US, being recently released from correctional facilities is associated with fatal overdose (18). Changes in the composition of illicit drugs can contribute to adverse health outcomes, including risk of overdose. Illicitly manufactured fentanyl, a synthetic opioid that is 50-100 times more potent than morphine, has contributed to the rising overdose rate in the US from opioids (19). Illicitly manufactured fentanyl is often sold as or mixed with heroin and other drugs, leading PWID to misjudge how much they can safely inject. In Baltimore, where heroin use has been entrenched for decades, the number of overdoses has dramatically risen, and has especially impacted the black community. From 2016-2017, the fatal overdose rate from fentanyl and other synthetic opioids increased by 61% among black Americans, compared with a 45% increase for whites (20). Access to community-based training and provision of naloxone, an opioid antagonist, can reduce fatal overdoses, but requires that PWID carry or have access to naloxone when needed. In a 2018 survey among 915 PWID in Baltimore, 46% reported receiving training in overdose prevention, 38% had received a supply of naloxone, 9% had administered naloxone, and only 9% reported usually carrying a supply of naloxone (21).

Opioids are not the only drug of choice for PWID. Indeed, 33% of PWID globally report primarily injecting amphetamine-type stimulants (ATS) (13). Likewise, there has been a geographical shift in the methamphetamine market. In 2015, the UN Office of Drugs and Crime
UNODC reported methamphetamine seizures in East and Southeast Asia eclipsed North American seizures for the first time, and local drug use patterns support increasing demand for methamphetamine(22). In 2017, the World Drug Report reported that among Thai PWID, HIV incidence was highest among methamphetamine users, with studies revealing that methamphetamine injection was independently associated with syringe sharing(23).

Epidemiology of HIV, HBV, and HCV among PWID

A 2017 systematic review estimated there to be 15.6 million PWID worldwide, with a global HIV prevalence of 17.8% (95% CI 10.8-24.8)(13). In the US, a 2014 meta-analysis estimated that there were 6.6 million PWID(24). Among US PWID, HIV prevalence is 10%. However, in Baltimore, 18% of PWID are infected with HIV(25). In Baltimore in 2017, IDU was the primary risk factor noted for 23.2% of males living with HIV, and 29% of females(26). An additional 6.5% reported being both MSM and PWID. Persistent racial disparities continue to exist in HIV prevalence in Baltimore – Black men were 11.1 times to be HIV-infected than white males, and black females were 20.3 times likely to be living with HIV than white females in the city(27).

In Thailand, HIV prevalence among PWID from 1996-2010 fluctuated between 35-52%; in the past decade, it has decreased to 20-25%(28). This decline is partially due to the drastic reduction in the estimated PWID population from 100,000-250,000 in 1994 to 40,500 in 2017, largely due to AIDS-related mortality. In 2006, antiretroviral therapy was added to the national health insurance scheme in Thailand. Despite increased access to ART, PWID often faced barriers in accessing HIV care, including stigma and discrimination from health care providers as
well as difficulty accessing or continuing therapy in prison. Indeed, although Thailand reports a high rate of coverage (80%) with ART, only 59% of HIV PWID were enrolled in ART from 2008-2013(29). Additionally, most PLHIV initiating ART have low CD4 counts (median 111, with 67% of newly initiating cases having CD4 under 200 in 2013). In 2014, Thailand recommended ART initiation regardless of CD4. However, disaggregated data on ART uptake has not been published on the coverage of PWID since that time.

Despite advances in HIV prevention, PWID continue to become infected with HIV at high rates. In 2017, one in 10 new HIV infections in the US were attributed to injecting drug use, similar to the UNAIDS estimate, where PWID represent 12% of all new infections globally(2). Demographic shifts in injecting globally have revealed that more women are injecting drugs, and 42% of new HIV cases diagnosed among PWID globally in 2018 were among women. The US experience mirrors this, with more injecting occurring in rural, white women. Women PWID often face unique risks that may not be faced by men who inject drugs. Many women report both first and subsequent injection by sexual partners, which has been associated with increased HIV risk. Because they may depend on their sexual partner for drugs (and injection), women are often “second on the needle,” and refusal to share injecting equipment or have condomless sex may be seen as not trusting their partner or denying intimacy (1, 30), and rejection can lead to increased rates of intimate partner violence (IPV). The syndemic of drug use and health-related risks is highlighted in West Virginia, where increasing substance use among women has led to the highest national rates of neonatal opioid withdrawal syndrome, drug overdose, acute hepatitis C, and acute hepatitis B(31).
While HIV prevention efforts have largely focused on injecting drug users, in certain contexts, non-injecting drug use can also contribute to increased HIV risk. The rise in use of amphetamine type stimulants (ATS), which includes amphetamine, methamphetamine, methylphenidate, and others, has been associated with increased sexual risk behavior in multiple key populations, including men who have sex with men (MSM) and female sex workers (FSW). In 2015, Thailand reported that methamphetamine was the most commonly used drug nationwide, and methamphetamine users made up the largest share of people seeking treatment for drug use(23). Increasing numbers of Bangkok-based Thai MSM report using ATS in the setting of sexual activity. In a prospective cohort study, ATS use was associated with incident HIV infection, sex work, group sex, and finding casual sex partners on the internet among MSM(32). In a Cambodian study, ATS users had more sex partners, higher levels of alcohol use, and increased risk of STI and HIV compared to non-ATS users(33). For both women who have sex with women (WSW) and MSM, ATS are often used in the setting of chemsex, defined as drug use intended to enhance, enable, or prolong sexual activity(34). MSM who use ATS have reported higher levels of risky receptive anal intercourse, condomless intercourse, and group sex(35). A review of MSM who reported ever using ATS found that they were 1.7-2 times more likely to be HIV infected than never users(36). In the US, the National Longitudinal Study of Adolescent Health revealed that non-injection crack cocaine users had 1.63 (95% CI 1.1-2.42) times the risk of becoming HIV infected, reported multiple sexual partners, and inconsistent condom use(37). As non-injecting and injecting drug users can engage in overlapping sexual risk networks, the transmission of HIV and STIs can also be amplified(38).
HBV Among PWID

In 2017, global HBV (defined as Hepatitis B surface antigen, or Hbsag positive) prevalence among PWID was calculated to be 9.1% (5.1-13.2%)(39). However, broad variation based on geography was noted. For example, more than half of all HbsAg-positive PWID reside in East and Southeast Asia. Among PWID in Northern Thailand who participated in a clinical trial of buprenorphine-naloxone use (HPTN 058) from 2007-2011, 13.9% were HbsAg positive at enrollment(40). Co-infection with HBV among all HIV-infected Thai patients has been estimated between 8-10%, and in people who do not use drugs, being MSM carries a higher risk of being HIV/HBV coinfected when compared to heterosexual men(41). In the US, HBV prevalence is concentrated among foreign-born individuals as widespread HBV vaccination has caused a decline in perinatal transmission(42). Despite this, acute HBV diagnoses increased 114% during 2009-2013 in Kentucky, Tennessee, and West Virginia, and was associated with increasing IDU activity in these areas(43).

HCV among PWID

Injecting drug use remains the leading cause of HCV acquisition and transmission in the US and in other global settings with access to safe blood supply and sterile medical equipment. HCV is at least 10 times as infectious as HIV and very efficiently transmitted through injecting. A serial cross-sectional cohort study of PWID in Baltimore demonstrated that most PWID acquired HCV within months after initiation of injection. In these cohorts sampled prior to the availability of ART, after ten months of injecting, 80% of PWID were infected with HCV, close to 60% were infected with HBV, and 20% with HIV(44). In 2017, the global HCV antibody prevalence among PWID was reported to be 52.3% (95% CI 42.4-62.1%)(13). In Thailand,
however, HCV prevalence is extremely high, with multiple studies reporting prevalence ranging from 60-90% through the mid-2000s(40, 45). However, a more recent study screening conducted from 2005-2010 among former or current PWID receiving methadone in Bangkok revealed a lower HCV antibody prevalence of 45%. In the US, incidence of HCV increased nearly 300% between 2010 and 2015(15). Acute hepatitis C diagnoses can often be a harbinger for increased HIV incidence, as hepatitis C is ten times more efficient at being transmitted through injection drug use(46). Indeed, 92.3% of the HIV cases identified during the Scott County, Indiana outbreak were co-infected with HCV, and molecular epidemiological analysis suggested that HIV acquisition was enabled by longstanding existing HCV transmission networks(47).

HCV prevalence among US PWID ranges from 70-90%. However, many PWID do not know their HCV status or have never been tested. Utilizing US insurance records, only 7.7% of PWID were tested for HCV from 2010-2017(48). As PWID are disproportionally affected by HCV, they comprise the majority of those living with HIV/HCV coinfection. Indeed, although 6.2% of people living with HIV globally are also co-infected with HCV, PWID are estimated to make up between 50-60% of all HIV/HCV coinfected people. In a large observational database combining HIV treatment databases in the Asia-Pacific Region, 15.2% of 7455 participants were HIV/HCV coinfected(41). A subset of these patients from Southeast Asian sites (Kuala Lumpur, Hanoi, Bangkok, and Jakarta) participated in an HIV/HCV coinfection study; 76% reported a history of IDU(49).
HIV/AIDS

As a clinical entity, AIDS was first described among men who have sex with men in Los Angeles in 1981, followed by reports of similar presentations among injecting drug users, hemophiliacs, and Haitians (50-52). Soon, health care institutions across the country, and then the world, were confronted with previously healthy patients who presented with rare diseases associated with severe immunosuppression, including Kaposi’s sarcoma, *Pneumocystis jiroveci* pneumonia, cryptosporidiosis, and mycobacterium infection. As no specific treatment existed at the time aside from supportive care, mortality was essentially universal. By 1983, human immunodeficiency virus (HIV) had been identified, and by 1984, over 38,000 cases had been reported from 85 countries (53, 54).

Classified as a lentivirus in the retrovirus family, HIV is the first virus identified to specifically target CD4+ cells. As HIV depletes the CD4+ population, people infected with HIV are unable to mount appropriate immune responses and become susceptible to a host of opportunistic infections.

In 1987, zidovudine, or AZT, was the first drug to be approved by the US Food and Drug Administration (FDA) for HIV treatment. A nucleoside reverse transcriptase inhibitor, it was able to slow disease progression when first initiated, and patients were able to reduce HIV viral replication, subsequently gaining weight and undergoing varying degrees of immune reconstitution. These effects remained short-lived, as HIV quickly mutated and became irreversibly resistant to the drug (55). As other anti-HIV drugs were discovered and tested in patients, it became clear that combination antiretroviral therapy, using multiple drugs with
different mechanisms of action, was most effective to suppress HIV replication, allow for
immune reconstitution, and decrease the emergence of resistance. A seminal presentation by
researchers at the 1996 Vancouver AIDS Conference promoted a combination of three drugs,
including protease inhibitors (approved in 1995), for those living with HIV(56).

While lifesaving, early antiretroviral regimens required those living with HIV to take
multiple pills, often two to three times a day. Adverse effects were also common, including
redistribution of fat (lipoatrophy and lipodystrophy), myopathy or peripheral neuropathy,
undesirable neuropsychiatric effects, hepatotoxicity, and blood cell dyscrasias.

Over the next two decades, HIV therapy has undergone dramatic changes. In 1996, only
five medications were approved in the US; in 2020, there are now 22 unique medications
approved for treatment of HIV. While side effects from long-term therapy still exist, a 20 year
old diagnosed with HIV in Switzerland in 2013 is now expected to live and additional 55 years,
compared to 12 years in the monotherapy era(57). Pill burden has been reduced to one pill a
day for many people living with HIV due to the increasing availability of co-formulated HIV
medications in fixed dose combinations. Notable advances in HIV treatment regimens include
tenofovir, a dually active HBV/HIV nucleoside reverse transcriptase inhibitor approved in 2001,
and the discovery of a new class of drugs, integrase inhibitors, in 2007. Currently, the fixed-dose
combination TLD (tenofovir, lamivudine, and dolutegravir) is recommended as first-line therapy
by the World Health Organization, and nearly 40% of those living with HIV globally are being
offered this combination(58).
Despite advances in antiretroviral treatment, lifelong treatment with daily oral medication still remains the standard of care for people living with HIV. Cure has been elusive as latently infected cells – known as the HIV reservoir – are difficult to identify and eliminate with current therapies. Research continues into longer-acting or injectable antiretrovirals for both HIV treatment as well as prevention. Promising long-acting agents in ongoing trials include an integrase inhibitor, cabotegravir, as well as islatravir, a nucleoside reverse transcriptase translocation inhibitor (59-61).

As HIV treatment has advanced, so has the field of HIV prevention. In 2016, after large global studies demonstrated that people with undetectable HIV RNA did not transmit HIV to their same-gender or opposite-gender sexual partners, the U=U (undetectable = untransmittable) campaign was launched (62, 63). The undeniable evidence that treatment as prevention works in preventing onward sexual transmission further bolsters the mandate to treat all those diagnosed with HIV as soon as possible after diagnosis.

Large-scale studies in multiple countries and contexts have shown the effectiveness of daily tenofovir and emtricitabine to prevent HIV infection in men who have sex with men, and the World Health Organization recommended PrEP to all MSM in 2014. In 2015, they expanded their recommendation to all high-risk populations, defined as those with an HIV incidence of 3% or higher (64). PrEP uptake has remained variable globally, but in settings where broad coverage among high-risk populations has been implemented, HIV incidence has been dramatically reduced (65). PWID have been largely left out of PrEP studies, with only one prospective trial – the Bangkok Tenofovir Study – specifically studying PrEP. In this study of 2400 PWID recruited
from Bangkok-based methadone centers, there was a 49% reduction in risk of HIV acquisition among those receiving tenofovir compared to placebo; in an analysis of those known to be taking tenofovir consistently, this increased to 74% (95% CI 16.6-94.0, p=0.03)(66).

Preventive vaccine trials have been largely disappointing, with only one trial - the RV144 trial in Thailand, conducted from 2003-2006 among over 16,000 people at community-level risk - demonstrating a 31.2% reduction in HIV diagnoses among those receiving the vaccine regimen compared to those who received placebo(67). While vaccine research continues, in January 2020, the data safety and monitoring board recommended that the largest preventive vaccine trial since RV144, HVTN 702, be halted. This trial, which recruited close to 6000 HIV negative participants across South Africa, had nearly equal numbers of HIV infections in the placebo (n=123) compared to the vaccine group (n=126) at the time of interim analysis, leading the DSMB to close the trial due to the ineffectiveness of the vaccine regimen at preventing HIV(68).

**Hepatitis B Virus**

Hepatitis B belongs to the Hepadnaviridae virus family and has a partially double stranded DNA genome. Although ten genotypes of HBV have been identified, the vast majority (approximately 96%) are of genotypes (A-E), and their distribution varies geographically. While genotyping was previously not conducted on a widespread basis, studies have shown that genotype can impact methods of transmission (such as vertical or horizontal), levels of chronicity, and liver disease progression. For example, genotypes C and D are more likely to progress to liver cirrhosis and hepatocellular carcinoma(69).
Humans are the only known host of hepatitis B. A bloodborne virus, transmission generally occurs through exposure of infected fluids through parenteral or mucosal routes. Globally, most people are infected in the perinatal period, either through vertical transmission or in the perinatal period. Other important modes of transmission include sexual contact or injecting drugs. Nosocomial infection can also occur through unsafe injection practices, or exposure to infected blood through procedures such as blood transfusion or hemodialysis.

Perinatal transmission is a very effective mode of HBV transmission. If the mother is highly infectious (both hepatitis B surface antigen (HbsAg) and hepatitis B e antigen (HbeAg) positive), between 70-90% of infants are infected through mother-to-child-transmission without postexposure prophylaxis. The vast majority, or up to 90%, of infants infected with HBV go on to develop chronic infection, compared to only 5% of immunocompetent adults who are exposed. Progression to chronic HBV infection depends on multiple factors, including age, immune status, and HBV genotype; those with HIV are less likely to spontaneously clear HBV (70). HBV infection can be categorized into different phases including inactive carrier, immune tolerant, and immune active. Inactive carriers have normal ALT and AST levels and minimal to no evidence of liver damage but can transmit HBV to others. Patients in the immune tolerant phase, characterized by elevated HBV DNA but low ALT levels, can undergo immune reactivation of HBV if immunosuppressed and return to an immune active phase. Those in the immune active phase, characterized by active liver inflammation, elevated HBV DNA, and fluctuating ALT levels require treatment to prevent ongoing liver damage.
An effective vaccine to prevent HBV acquisition was licensed and approved in the early 1980’s, with recombinant HBV vaccine becoming available in the US in 1986. The standard three-dose regimen is recommended to be given at 0, 1, and 6 months, and has between a 80-100% vaccine effectiveness rate among those with normal immune systems. Immunogenicity decreases with age – while over 95% of children mount protective antibody responses, this decreases to 90% of normal 40-year olds and 75% of 60-year olds. HIV-infected adults have also had a lower rate of response to HBV vaccination with response rates ranging between 50-80% depending on the population studied(71, 72). A new HBV vaccine, HEPLISAV-B, was approved in 2017 and is administered as a two-dose regimen at 0 and 1 months. This regimen utilizes a TLR8 adjuvant and is more effective than the prior 3 dose regimens in those with normal immune systems(73); trials among HIV-infected adults are scheduled to start enrollment in 2020.

In the US, although hepatitis B vaccination was originally recommended for groups deemed to be at high risk of HBV acquisition in 1982, including men who have sex with men and injection drug users, it was not widely administered until the 1990s. Infant vaccination was recommended in November 1991, followed by catch-up dosing for previously unvaccinated adolescents (age 11-12) in 1995 and then for all previously unvaccinated minors (under age 18) in 1999(74). Despite recommendation for all HIV-infected individuals who are not immune to hepatitis B receive immunization, only 9.6% of eligible individuals initiated vaccination in a US-based cohort of HIV clinics between 2009-2012(75).

For individuals who develop chronic HBV, there is currently no curative treatment. However, effective antiviral medications are available that suppress HBV replication. Many of
these medications are also effective against HIV and are therefore recommended for HIV/HBV co-infected individuals as part of their ART regimen. Lamivudine, an HIV nucleoside reverse transcriptase inhibitor and HBV polymerase inhibitor, was originally approved for use by the FDA in 1995. It is one of the most widely used antivirals used globally in the treatment of HIV and HBV due to its low cost and minimal side effect profile. Unfortunately, lamivudine has a low genetic barrier to resistance, and monotherapy leads to increasing resistance over time, independent of other factors such as baseline HBV DNA level prior to therapy. In one study of HIV/HBV co-infected patients on lamivudine as part of their antiretroviral regimen, approximately 50% had resistance after two years of therapy, with the number climbing to 90% after four years of treatment(76). Emtricitabine, a cytidine analogue, was approved by the US FDA in 2003 and is structurally very similar to lamivudine, with nearly identical resistance patterns. Due to the high levels of resistance when utilized as monotherapy, neither lamivudine nor emtricitabine are approved for hepatitis B therapy by the US FDA. However, they are still widely used globally as first-line treatment for HBV-infected patients.

Tenofovir, a nucleotide reverse transcriptase inhibitor, is currently recommended as standard of care for treatment of both HIV and HBV in co-infected patients. It was approved by the US FDA in 2001, and co-formulations with emtricitabine was approved in 2004. For both viruses, tenofovir has potent antiviral activity and a high genetic barrier to resistance. For HBV specifically, tenofovir is effective against lamivudine-resistant HBV(77). Two other antivirals used for HBV mono-infection, entecavir and adefovir, cannot be used for treating HIV, and there are high rates of failure when used to treat lamivudine-resistant HBV(78). In a meta-
analysis of tenofovir use, a majority of HIV/HBV coinfected patients suppress HBV DNA levels to an undetectable level after at least two years of therapy (79). Additionally, HBV resistance has not been documented in either HBV mono-infected or HIV/HBV coinfected patients on tenofovir therapy (80). However, prolonged tenofovir therapy can cause proximal tubular dysfunction, worsening of chronic kidney disease, and bone loss. Due to these side effects, tenofovir alafenamide (TAF), with less nephrotoxicity, was introduced in 2015 as part of fixed-dose combinations with other antivirals effective against HIV; in 2016, it was made available as a treatment for chronic hepatitis B mono-infection (81-83).

While tenofovir is generally well-tolerated, research continues to identify novel approaches to hepatitis B cure. While complete eradication of hepatitis B virus is unlikely due to difficulty in eradicating the covalently closed circular DNA (cccDNA) of HBV in the nucleus of infected hepatocytes and the stability of HBV genome, functional cure, defined as sustained loss of hepatitis B surface antigen with or without hepatitis B surface antibody seroconversion has become widely accepted by the scientific community as a feasible goal (84, 85). Functional cure is associated with improved clinical outcomes, including decreased liver inflammation and reduced rates of hepatocellular carcinoma (86). Agents currently under investigation include those that modify immune response to HBV such as checkpoint inhibitors and TLR8 agonists as well as direct acting antivirals that target capsid assembly or interfere and destroy viral RNA (87). However, the timeline for these therapies to be approved is estimated to be five to ten years.
Hepatitis C Virus

Hepatitis C belongs to the Flaviviridae family and is a single stranded RNA virus. Based on genome sequencing, HCV is categorized into seven genotypes and multiple subtypes. HCV transmission most often occurs through blood, and is most effectively transmitted through use of contaminated needles, syringes, or blood products. Other modes of transmission have been identified but are less efficient than bloodborne transmission. These include sexual transmission among men who have sex with men and perinatal transmission. Perinatal transmission occurs at a much lower rate than HBV transmission, with transmission occurring in approximately 5% of viremic mothers(88). Mothers who are co-infected with HIV are more likely to transmit.

The genotypic distribution of HCV differs based on geography. In the US, around 75% of individuals infected with HCV had genotype 1 infection, with genotypes 2 and 3 representing about 10% of HCV infections. In Thailand, there is more diversity in HCV genotypes, with the most predominant genotype being 3 (~40%), followed by genotype 1 (~30%), and then genotype 6(89).

Unlike HBV, 70-80% of those who are exposed to HCV will develop chronic infection; individuals who were previously infected with HIV have been noted to have even lower rates of spontaneous clearance despite being on antiretroviral therapy. Prior to 2013, treatment for HCV consisted of treatment with both ribavirin and interferon. This regimen was onerous and generally required a minimum treatment length of 24 weeks to a maximum of 48 weeks. In addition to requiring weekly injections, side effects from interferon and ribavirin were common,
and led to premature discontinuation or noncompliance from many patients. These side effects included flu-like symptoms, neutropenia, anemia, and neuropsychiatric effects such as new-onset depression or exacerbation of previous psychiatric disorders. Treatment efficacy is determined by measurement of HCV RNA a standard number of weeks following cessation of treatment. If no HCV RNA is detected, then the patient is said to have achieved sustained virological response (SVR), or HCV cure. During the interferon era, SVR was measured 24 weeks after cessation of treatment and depended on both host (IL28B genotype) and viral (HCV genotype) factors. While HCV genotypes 2 and 3 had SVR rates in the 80-90% range with interferon-containing regimens, HCV genotype 1 had poorer response rates, in the 50% range. Additionally, those with IL28B CC genotype had the highest SVR rates regardless of HCV genotype, with TT and CC genotypes predicting lower response rates to pegylated interferon and ribavirin. IL28B CC genotype was most prevalent among Asians (90-100%) and least prevalent among those with African ancestry (23-55%) (90). Racial disparities in response to treatment persisted beyond genotype alone, however. African Americans, for example, had only a 53% chance of achieving SVR with CC genotype, compared to 77% for Hispanic Americans and 82% for European Americans (91).

Telaprevir and boceprevir, serine protease inhibitors, were approved by the US FDA in 2011 for genotype 1 patients. However, monotherapy was ineffective and led to emergence of drug resistance, so treatment with these new agents still required the use of interferon and ribavirin. With this combination, those with genotype 1 achieved 20-30% increases in SVR compared to regimens containing pegylated interferon and ribavirin alone. Side effects,
including rash and anemia, often limited patient tolerability and treatment, and often led to premature discontinuation of therapy in HIV/HCV coinfected patients (92).

In 2013, the discovery and approval of sofosbuvir NS5A inhibitor by the US FDA, marked a shift to the direct-acting antiviral (DAA) era. DAA dissemination in the US was delayed until after 2015, but revolutionized HCV treatment. While sofosbuvir was originally used with pegylated interferon and ribavirin, other DAAs were quickly discovered and approved, and allowed for HCV treatment to be administered as all oral regimens, for a much shorter treatment period (generally 8-12 weeks), and with minimal side effects (93). However, certain combinations, such as sofosbuvir/ledipasvir and elbasvir/grazepevir, were only approved for certain genotypes due to decreased efficacy based on genotype (94, 95). Trials demonstrated equal efficacy among HIV/HCV coinfected compared to HCV mono-infected patients alone (93, 96, 97). Some DAA combinations, such as sofosbuvir/velpatasvir, sofosbuvir/daclatasvir, and glecaprevir/pibrentasvir, showed high SVR rates across all genotypes, allowing DAAs to be prescribed without prior HCV genotyping (98-100). Finally, SVR could now be measured 12 weeks following completion of treatment. All of these advances led to SVR rates surging to >90-95% for all genotypes.

No preventive vaccine for HCV currently exists. Unfortunately, the first human trial testing a prophylactic vaccine regimen consisting of a recombinant chimpanzee adenovirus 3 vector vaccine prime followed by a recombinant vaccinia Ankara virus boost did not reduce HCV incidence in HCV negative PWID; both groups had HCV incidence of 14.1 infections per 100 person-years (101).
Specific aims

The following chapters highlight various aspects of how substance use and co-infection with viral hepatitis can impact clinical outcomes of patients living with HIV in Baltimore, Maryland and Bangkok, Thailand. The first two papers utilized data from the Johns Hopkins HIV Clinical Cohort. As approximately 75% of cohort participants report ever injecting drugs, coinfection with viral hepatitis is common. The final paper utilized data from the RV254/SEARCH010 cohort in Bangkok, Thailand. This cohort, established in 2009, is largely comprised of MSM who were diagnosed with acute HIV infection from HIV testing done at the Thai Red Cross Anonymous Clinic. Injecting drug use is rare in this population; however, ATS use among the MSM population in Bangkok has increased over the past five years.

In the first paper titled “Barriers to HCV treatment initiation in patients with HIV/HCV coinfection: Lessons from the interferon era,” we investigate factors associated with initiation of HCV treatment among HIV/HCV coinfected patients during the interferon era, prior to the discovery and approval of all oral, DAA regimens. When DAAs were initially approved, HCV elimination was thought to be within reach as interferon was viewed to be the rate-limiting factor for HCV treatment among many populations. Utilizing a case-control design, we elucidate factors that would not be substantially impacted with the removal of interferon, underscoring the need to address other factors to improve the HCV treatment cascade among HIV/HCV coinfected patients.

In the second paper titled “Coinfection with Hepatitis C and/or Hepatitis B virus is associated with reduced survival among people living with HIV in early and later antiretroviral
treatment eras,” we investigate the impact of co-infection with HBV, HCV, or both on the survival of patients living with HIV before and after the introduction of HBV-active ART (tenofovir) and HCV therapy (pegylated interferon), and explore factors associated with increased mortality in coinfected populations. Additionally, we characterize cause-specific mortality among HIV, HIV/HBV, HIV/HCV and HIV/HBV/HCV coinfected patients to examine whether or not liver related mortality decreased among co-infected patients following introduction of HBV- and HCV- specific therapies. This analysis provides evidence into other causes of mortality that may differentially affect co-infected populations.

In the third paper titled “Group sex and methamphetamine use fuel an explosive epidemic of Hepatitis C among HIV-infected men who have sex with men in Bangkok, Thailand,” we describe increasing HCV incidence rates among a predominantly Thai MSM cohort who were diagnosed with acute HIV infection. By elucidating factors associated with HCV incidence, we reveal high-risk behaviors that can amplify HCV transmission in this key population. The findings from this study emphasizes the urgent need for increased access to integrated HCV treatment within HIV care settings to both 1) prevent morbidity and mortality associated with HCV and 2) decrease onward transmission.
Chapter 2:
Barriers to HCV treatment initiation in patients with HIV/HCV coinfection: Lessons from the interferon era
Abstract

Background  Hepatitis C is a major cause of mortality among HIV infected patients, yet HCV treatment uptake has historically been low. While the removal of interferon removes a major barrier to HCV treatment uptake, oral therapies alone may not fully eliminate barriers in this population.

Methods  Within the Johns Hopkins Hospital HIV cohort, a nested case-control study was conducted to identify cases, defined as patients initiating HCV treatment between January 1996 and 2013, and controls, which were selected using incidence density sampling (3 to 1 ratio). Controls were matched to cases on date of enrollment. Conditional logistic regression was used to evaluate factors associated with HCV treatment initiation.

Results  Among 208 treated cases and 624 untreated controls, the presence of advanced fibrosis (OR 2.23, 95% 1.26, 3.95 and non-black race (OR 2.01, 95% CI 1.26, 3.20) were independently associated with initiation of HCV therapy. Recent active drug use (OR 0.36, 95% CI 0.19, 0.69) and an increasing proportion of missed visits was independently associated with lower odds of HCV treatment (25-49% missed visits [OR 0.49, 95% 0.27, 0.91] and ≥ 50% missed visits [OR 0.24 (0.12, 0.48).

Conclusion  Interferon-free treatments may not be sufficient to fully overcome barriers to HCV care in HIV-infected patients. Interventions to increase engagement in care for HIV and substance use are needed to expand HCV treatment uptake.
Introduction

Chronic hepatitis C virus (HCV) infection is a leading cause of cirrhosis and hepatocellular carcinoma, and since 2007, HCV has superseded HIV as a cause of death in the United States (102). Due to shared routes of transmission, HCV and HIV epidemics often overlap (103, 104). Up to 25% of all HIV-infected individuals in the United States are coinfected with HCV, with coinfection rates as high as 90% among persons who inject drugs (PWID) (105). When compared to HCV monoinfected individuals, co-infected patients have accelerated progression of liver disease and increased risk for liver-related morbidity and mortality (106, 107).

HCV treatment can eradicate infection, and sustained virological response (SVR), defined as undetectable HCV RNA in the blood twelve weeks after the completion of HCV treatment, is strongly associated with reduced risk of liver-related morbidity and mortality. Among HIV/HCV coinfected patients, HCV treatment in the era of interferon-based regimens was marked by poor tolerability, frequent serious adverse events, complex drug interactions, and limited efficacy with SVR rates of 20 to 29% in patients with HCV genotype 1 infection. Not surprisingly, in this context, HCV treatment uptake was limited (108-113).

In 2014, interferon-free, direct acting antiviral (DAA) regimens were approved by regulatory authorities for the treatment of HCV genotype 1 infection based on clinical trials in which more than 95% of patients achieved SVR after 12 weeks of oral treatment (93, 114-116). Importantly, the safety, tolerability, and efficacy of these DAA regimens have been similar in persons with and without HIV coinfection (96, 117-119). While these treatments represent a
significant breakthrough, the removal of interferon may not fully eliminate barriers to HCV cure in persons with HIV/HCV coinfection. To investigate potential residual barriers to HCV treatment in the oral DAA era, we conducted a nested case-control study to identify factors associated with the initiation of interferon-based HCV treatment in HIV/HCV coinfected patients receiving primary HIV care in an urban HIV clinic. We hypothesized that while the removal of interferon is necessary to increase rates of HCV cure, other barriers to HCV treatment remain and interferon-free, DAA regimens alone will not be sufficient to eliminate HCV in this HIV/HCV co-infected patient population.

**Methods**

A nested case-control study was conducted within the Johns Hopkins Hospital HIV Clinic cohort, an urban, Baltimore-based cohort with high rates of injecting drug use and low socioeconomic status. The cohort has followed approximately 8,000 patients annually since 1996 (120). Cases were defined as coinfected patients initiating their first course of HCV treatment with interferon and ribavirin between January 1996 and January 2013. Controls were selected using incidence density sampling in a ratio of 3 to 1 and were matched to cases on date of HIV clinic enrollment (+/- six months). Controls were eligible if they had confirmed HCV infection and had not received HCV treatment at the time of matching. HCV infection was considered confirmed if an individual had reactive HCV antibody and either detectable HCV RNA or no available HCV RNA testing. Patients with reactive HCV antibody and undetectable HCV RNA were excluded as they would not have been considered for HCV treatment.
Data on patient demographics, health-related behaviors (e.g. drug and alcohol use), prescribed medications, and laboratory tests were abstracted from medical records. For cases and controls, time-varying characteristics were assessed within a six-month window of the date of HCV treatment initiation of the case. Laboratory assessments, conducted by licensed clinical laboratories, included complete blood cell count, serum chemistry panel, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, CD4 cell count, HCV genotype, and plasma HIV-1 RNA. AST, ALT, platelets, albumin, and bilirubin were categorized according to Division of AIDS toxicity grades for adverse events. HIV-1 RNA was defined as undetectable if values were below 400 copies/mL. To assess liver disease stage, the FIB-4 index was used to categorize patients using validated criteria for minimal liver disease and cirrhosis (121).

Conditional logistic regression was used to evaluate factors associated with HCV treatment initiation. A series of multivariate models were constructed to evaluate factors that were significant (p<0.05) in the univariate analysis. All models included age, sex, and race regardless of statistical significance. Due to collinearity between genotype and race, only race was included in the models. A sensitivity analysis was conducted to address the issue of missing data in the covariates included in the multivariate model. Multiple imputation with chained equations was used and 40 imputed datasets were created. Inferences from the analysis using multiple imputation did not differ from the complete case analysis. All analyses were conducted using Stata 12 (StataCorp LLC, College Station, Texas).
All procedures and protocols for this study were reviewed and approved by the Johns Hopkins Institutional Review Board. Written informed consent was obtained from all patients.

**Results**

*Patient population.*

The majority of treated patients (cases) were male (68%) and black (77%), and had a median age of 47.5 years (Table 1). Untreated patients (controls) were similar with respect to sex (male, 68%) and age (median 46.6 years), but a higher proportion (89%) were black. Compared to untreated patients, treated patients had a higher CD4 count at time of HCV treatment initiation, 468 cells/mm$^3$ versus 339 cells/mm$^3$. Although the proportion of treated and untreated patients prescribed antiretroviral therapy was similar, 81% vs. 76% (Odds Ratio [OR] 1.29, 95% CI 0.79, 2.11), HIV RNA suppression was higher in treated patients (74%) compared to untreated patients (64%) (OR 1.78, 95% CI 1.21, 2.62).

Treated and untreated patients had a similar number of average HIV primary care visits per year prior to HCV treatment initiation (median 7.0 visits vs. 6.1 visits, OR 1.02, 95% CI 0.99, 1.06). However, untreated patients were significantly more likely to have missed scheduled clinic appointments in the past year compared to treated patients. Compared to treated patients, untreated patients who missed up to 25% of their scheduled visits in the preceding year were 40% less likely to be treated (OR 0.59, 95% CI 0.32-1.09); this increased to 67% in those who missed between 25-49% of their appointments (OR 0.33, 95% CI 0.18, 0.61) and 83% in those who missed 50% or more of their appointments (OR 0.17, 95% CI 0.09, 0.33).
The majority of treated (71%) and untreated (78%) patients reported ever using injection drugs and alcohol. However, at the last visit prior to HCV treatment initiation, treated patients were significantly less likely than untreated patients to report active drug use (OR 0.27, 95% CI 0.15, 0.49) and were also likely to report active alcohol abuse (OR 0.45, 95% CI 0.25, 0.82). Of note, the diagnosis of comorbid psychiatric disease was more common among treated patients (77% vs. 68%); however, among all patients with psychiatric disease, treated patients were more likely to be actively engaged in psychiatric care in the co-localized mental health clinic compared to untreated patients (40% of treated versus 29% of untreated patients).

With respect to HCV infection, the majority of both treated and untreated patients were infected with HCV genotype 1 (94% vs. 97%, respectively). HCV genotype varied according to self-reported race; the prevalence of HCV genotype 1 infection was 99% and 80% among black and non-black patients, respectively. Non-black patients were more likely to be infected with HCV genotypes 2 or 3, and patients with these genotypes were more likely to be treated. As assessed by FIB-4 serum index, treated patients were more likely to be classified as having advanced liver disease than those not treated (Table 1).

Predictors of HCV Treatment initiation.

In univariate analysis, non-black race, non-HCV genotype 1 infection, and markers of more advanced liver disease (FIB-4 > 3.25) were significant predictors of HCV treatment initiation (Table 1). Adherence to HIV care visits, defined as the ratio of attended to scheduled clinic visits (proportion of missed scheduled visits), successful receipt of antiretroviral therapy defined by HIV-RNA suppression (HIV-RNA<400 copies/ml), and engagement in psychiatric care
were also positively associated with the initiation of HCV treatment. In contrast, self-report of active drug or alcohol use were strongly associated with not receiving treatment. After adjustment for confounders, the presence of advanced liver disease (FIB-4 score>3.25), self-reported active drug use and non-black race were independently associated with initiation of HCV treatment (Table 2). Adherence to scheduled HIV clinic visits in the year prior to HCV treatment was a strong, independent predictor of HCV treatment in multivariate analysis with an increasing percentage of missed, scheduled visits (no-shows) associated with a lower odds of treatment.

**HCV Treatment Outcomes.**

Of the 208 HIV/HCV coinfected patients who initiated treatment with interferon/ribavirin, 17.8% achieved SVR. Among those who failed to achieve SVR, on-treatment virologic non-response was reported in 70.7% and post-treatment viral relapse was observed in 7.2% of those treated; virologic outcomes were unknown the remaining patients (4.3%). Of note, only three patients had documented treatment discontinuation due to adverse events or other non-virologic factors.

**Discussion**

With the advent of safe and efficacious DAA regimens, there is great potential to increase the proportion of HIV/HCV coinfected patients who achieve HCV cure, leading to decreased risk of liver-related morbidity and mortality. Indeed, based on the achievement of SVR in more than 95% of HCV genotype 1/HIV coinfected patients treated with interferon-free, oral DAA regimens in clinical trials, the American Association for the Study of Liver Disease
(AASLD)/Infectious Diseases Society of America (IDSA) HCV guidance panel recommended that all coinfected patients be treated for hepatitis C including those at high risk for transmission of HCV to others (97, 117, 118, 122). While the selection of coinfected patients for HCV treatment has been markedly simplified in the DAA era, our findings on treatment initiation in the interferon era may have important implications for the potential elimination of HCV in populations with HIV/HCV co-infection.

First, we did not find evidence that psychiatric disease or medical comorbidities such as chronic kidney disease were associated with decreased uptake of interferon-based therapy. On the contrary, we found that a higher percentage of treated patients had been previously diagnosed with comorbid psychiatric disease; engagement in mental health care available onsite in the HIV clinic was associated with greater likelihood of initiating HCV treatment. This finding suggests that mental illness did not represent an independent barrier to HCV treatment in the interferon era in this particular clinic, as mental health services were integrated with HIV care. In other settings where mental health services are not as accessible, the removal of interferon may have an even larger beneficial effect, as DAAs provide more tolerable and safer treatment in persons with depression and other psychiatric conditions.

Second, we observed a strong dose-response relationship between the proportion of missed visits (no shows) and the likelihood of HCV treatment. After adjustment for confounders, compared to treated patients who kept scheduled visits in the preceding year, patients who missed between 25 and 49% of their scheduled visits and those who missed 50% or more of scheduled visits were 67% and 83% less likely to start HCV treatment. Indeed, this
measure of missed visits was a stronger predictor of HCV treatment initiation than actual attendance at clinic visits, and mirrors previous observations in HIV care, where missed clinic visits has been linked to lack of HIV suppression with antiretroviral therapy. For example, in the Johns Hopkins HIV clinic, Lucas and colleagues demonstrated that missed visits were associated with HIV treatment failure in the early ART era(123). More recently, in the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) multisite HIV cohort, Mugavero and colleagues found that missed primary HIV care visits following ART was a strong predictor of retention in HIV care and, more importantly, of mortality (124).

The finding that increasing numbers of missed HIV care visits strongly predicts low HCV treatment initiation has implications for the DAA HCV treatment era because the removal of interferon from the regimen will not address this important barrier to HCV treatment uptake. This observation also highlights the need to focus on linking and retaining co-infected patients in HIV care by working to reduce missed visits for both HIV and concurrent mental health conditions. In addition, along with measures of adherence to HIV treatment (e.g., viral suppression, or an undetectable HIV RNA), the rate of missed visits may be useful in clinical practice to identify persons for whom additional support may be needed to successfully engage in HCV care.

Third, coinfected patients who were not treated for HCV were more likely to have recently used illicit drugs and/or alcohol. These factors are known to be associated with poor adherence to clinic visits and medical treatment(125). The impact of this barrier on HCV care may be mitigated by the short duration of HCV treatment (12 weeks) needed to achieve HCV
cure in most coinfected patients. However, the HCV care continuum extends beyond the short treatment course for HCV, and patients with cured HCV continue to require monitoring for liver disease progression and re-infection. Ongoing alcohol use may contribute to progressive liver disease despite HCV cure. Additionally, patients who engage in high-risk behaviors such as unprotected sex or injection drug use following SVR are at risk for HCV re-infection. In a meta-analysis examining rates of HCV reinfection after curative treatment, Simmons and colleagues reported that the five-year risk of reinfection may be as high as 21.8% among HIV/HCV coinfected patients (126). Importantly, in one study of young PWID, opioid substitution therapy was independently associated with a lower hazard of incident HCV infection even after adjustment for incarceration and homelessness (127). Our finding suggests that drug and alcohol abuse will continue to be important issues in the era of oral DAAs both as major contributors to missed appointments and as risk factors for ongoing liver disease (alcohol) and re-infection (injection drug use) after HCV cure is achieved. Taken together, our data strongly support the close linkage of programs to treat HIV, hepatitis C and addiction; importantly, harm reduction interventions must extend beyond the short HCV treatment period.

Finally, our data reveal racial disparity in the provision of HCV treatment in the interferon era. Lower treatment uptake among black patients in our cohort could in part be due to the greater prevalence of genotype 1 infection, which was more difficult to treat with interferon. Genotype notwithstanding, black patients were also less likely to respond to interferon-based treatments than white patients due, in part, to the presence of unfavorable interferon lambda 4 polymorphism (90, 91). In this context, many health care providers and
black patients with HCV genotype 1 infection may have been unwilling to initiate treatment with interferon/ribavirin. Other medical factors may also have precluded HCV treatment with interferon. In the IDEAL study of peginterferon/ribavirin, blacks were less likely than non-blacks to meet eligibility criteria, largely due to higher prevalence of neutropenia and uncontrolled medical conditions such as diabetes or chronic renal insufficiency (128). Thus, it is possible that the observed racial disparity in our study is explained by the inability of blacks to use interferon-based treatments due to unfavorable genotypes or polymorphisms and/or medical comorbidities. If this is the case, the removal of interferon and the use of highly effective, oral DAA regimens may result in similar treatment uptake among blacks and non-blacks (129). However, it is also possible that the observed disparity in HCV treatment initiation may not be fully explained by the use of interferon alone. In the Veterans Affairs healthcare system, black veterans were still less likely to undergo HCV treatment compared to non-black veterans in the DAA era (130). Similar racial disparities have been observed in the treatment of HIV infection and may in part be explained by a higher rate of missed visits among black patients in HIV care (131). Other factors, including general mistrust of the medical system, providers, and treatments have also been associated with lower adherence to antiretrovirals among black patients, and may also be important contributors to decreased HIV engagement in care (132). Thus, while more effective interferon-free HCV treatments are necessary, they may not fully overcome racial disparities in HCV care, highlighting the need for targeted, culturally appropriate interventions to engage black patients with HIV/HCV coinfection.
This study has some limitations. First, alcohol and illicit drug use were self-reported, and chart review noted that data was missing for both cases and controls when the physician did not actively include this in documentation. Second, the decision to initiate or forego HCV treatment is complex and likely subject to additional factors from both the provider and patient perspective that we were unable to measure. Further, these intangible factors underlying the selection of patients for HCV treatment are likely to be different in the DAA era. Nonetheless, the barriers that we observed to HCV treatment are consistent with previously reported barriers to engagement in HIV and HCV care and support the validity of our findings. Third, access to HCV treatment was generally not restricted by payers in the interferon era and we did not note a difference in type of health insurance coverage between treated and untreated patients in our study. In contrast, in the DAA era, limited access by payers is undoubtedly an important barrier to HCV treatment. Lastly, our findings are derived from a single, urban HIV clinic; however, the demographics of our cohort is similar to that of many inner-city HIV infected populations, to which our study findings may be generalizable.

In conclusion, while the availability of safe and effective, interferon-free HCV treatment regimens is necessary to increase the rate of HCV treatment in coinfected patients, our findings indicate that DAA regimens alone cannot be expected to completely overcome barriers to HCV cure in this patient population. To improve the HCV care continuum and prevent ongoing HCV transmission, efforts may be best focused on increasing the engagement of coinfected patients in medical care for their HIV infection, comorbid mental illness, and/or active drug or alcohol abuse. In the United States, further research is also needed to address the potential for the
persistence of racial disparities in the delivery and uptake of highly effective, all-oral, interferon-free HCV treatment.

Note: This paper was published as a first author manuscript in Open Forum for Infectious Diseases in 2017(133)
<table>
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<tr>
<th>Characteristic</th>
<th>Cases N=208 (%)</th>
<th>Controls N=624 (%)</th>
<th>Crude OR (95% CI)</th>
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<td>423 (68)</td>
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<td>White</td>
<td>44 (21)</td>
<td>66 (11)</td>
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<tr>
<td>Other</td>
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<td>4 (1)</td>
<td>3.44 (0.85, 13.85)</td>
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<td>2</td>
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<td>339 (189, 530)</td>
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<td>% of missed HIV care appointments in the past year</td>
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<tr>
<td>-----------------------------------------------</td>
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<td>14 (7)</td>
<td>120 (22)</td>
<td>0.27 (0.15, 0.49)</td>
</tr>
<tr>
<td>Missing</td>
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<td>89</td>
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<tr>
<td>Health insurance</td>
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<tr>
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<td>118 (57)</td>
<td>326 (53)</td>
<td>1.0</td>
</tr>
<tr>
<td>Medicaid/Medicare</td>
<td>65 (31)</td>
<td>211 (34)</td>
<td>0.85 (0.59, 1.21)</td>
</tr>
<tr>
<td>None</td>
<td>25 (12)</td>
<td>83 (13)</td>
<td>0.83 (0.51, 1.36)</td>
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<tr>
<td>FIB-4 score†</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt;1.45</td>
<td>89 (44)</td>
<td>261 (53)</td>
<td>1.0</td>
</tr>
<tr>
<td>1.45-3.25</td>
<td>75 (37)</td>
<td>177 (36)</td>
<td>1.27 (0.87, 1.84)</td>
</tr>
<tr>
<td>&gt;3.25</td>
<td>39 (19)</td>
<td>56 (11)</td>
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<tr>
<td>Missing</td>
<td>5</td>
<td>130</td>
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<tr>
<td>Alanine aminotransferase, U/L (Median, IQR)</td>
<td>62 (36, 97)</td>
<td>38 (25, 62)</td>
<td></td>
</tr>
<tr>
<td>Grade 0</td>
<td>80 (39)</td>
<td>328 (66)</td>
<td>1.0</td>
</tr>
<tr>
<td>Grade 1</td>
<td>78 (38)</td>
<td>133 (27)</td>
<td>2.23 (1.52, 3.27)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>34 (17)</td>
<td>30 (6)</td>
<td>4.78 (2.63, 8.70)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>8 (4)</td>
<td>6 (1)</td>
<td>6.96 (2.12, 22.84)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>3 (1)</td>
<td>1 (&lt;1)</td>
<td>12.21 (1.21, 123.46)</td>
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<tr>
<td>Missing</td>
<td>5</td>
<td>126</td>
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### Hemoglobin, grams/dL (Median, IQR)

<table>
<thead>
<tr>
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<th>&lt;10</th>
<th>≥10</th>
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<tbody>
<tr>
<td>Median</td>
<td>13.6</td>
<td>13.0</td>
</tr>
<tr>
<td>IQR</td>
<td>(12.4, 14.9)</td>
<td>(11.7, 14.4)</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>&lt;10</th>
<th>≥10</th>
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<tbody>
<tr>
<td>Count</td>
<td>3 (1)</td>
<td>29 (6)</td>
</tr>
<tr>
<td></td>
<td>0.17 (0.04, 0.72)</td>
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<tbody>
<tr>
<td>Missing</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>105</td>
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</table>

### Platelet, count/mm³ (Median, IQR)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Median</td>
<td>188 (139, 232)</td>
</tr>
<tr>
<td>IQR</td>
<td>201 (154, 246)</td>
</tr>
</tbody>
</table>

### Serum Creatinine, mg/dL

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>≤1.1</td>
<td>168 (86)</td>
</tr>
<tr>
<td></td>
<td>410 (79)</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
</tr>
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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>1.2-2.0</td>
<td>26 (13)</td>
</tr>
<tr>
<td></td>
<td>94 (18)</td>
</tr>
<tr>
<td></td>
<td>0.69 (0.43, 1.11)</td>
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<tr>
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<th></th>
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<tbody>
<tr>
<td>&gt;2.0</td>
<td>2 (1)</td>
</tr>
<tr>
<td></td>
<td>15 (3)</td>
</tr>
<tr>
<td></td>
<td>0.34 (0.08, 1.57)</td>
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<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Missing</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>105</td>
</tr>
</tbody>
</table>

**Abbreviations:** ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; FIB, fibrosis; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IQR, interquartile range; OR, odds ratio; PLT, platelet; ULN, upper limit of the normal

The grade of the alanine aminotransferase (ALT) levels was based on an upper limit of the normal (ULN) range of 40 Units/L as follows: Grade 0 < 1.25 x ULN; Grade 1 = 1.25 to 2.5 x ULN; Grade 2 = 2.6 to 5.0 x ULN; Grade 3 = 5.1 to 10 x ULN; Grade 4 ≥ 10 x ULN.

*Odds ratio is for the comparison of HCV genotype 1 to all other HCV genotypes

†FIB-4 score was calculated using the following formula: age [years] x AST [U/L]/((PLT [109/L]) X (ALT [U/L])/1/2).
### TABLE 2-2: Multivariate Analysis of HCV Treated Patients (Cases) vs. HCV Untreated Patients (Controls)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Complete case analysis</th>
<th>Multiple imputation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted OR (95% CI)</td>
<td>Adjusted OR (95% CI)</td>
</tr>
<tr>
<td>Male</td>
<td>0.95 (0.61, 1.50)</td>
<td>0.89 (0.62, 1.29)</td>
</tr>
<tr>
<td>Age</td>
<td>0.98 (0.94, 1.02)</td>
<td>0.99 (0.97, 1.02)</td>
</tr>
<tr>
<td>Non-black race</td>
<td><strong>2.47 (1.36, 4.47)</strong></td>
<td><strong>2.01 (1.26, 3.20)</strong></td>
</tr>
<tr>
<td>Self-reported illicit drug use at last visit</td>
<td>0.52 (0.25, 1.08)</td>
<td><strong>0.36 (0.19, 0.69)</strong></td>
</tr>
<tr>
<td>% missed primary care visits in last year</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>0-24</td>
<td>0.78 (0.38, 1.60)</td>
<td>0.76 (0.41, 1.42)</td>
</tr>
<tr>
<td>25-49</td>
<td><strong>0.41 (0.20, 0.83)</strong></td>
<td><strong>0.49 (0.27, 0.91)</strong></td>
</tr>
<tr>
<td>≥50</td>
<td><strong>0.21 (0.09, 0.46)</strong></td>
<td><strong>0.24 (0.12, 0.48)</strong></td>
</tr>
<tr>
<td>Undetectable HIV-RNA</td>
<td>1.26 (0.77, 2.06)</td>
<td>1.43 (0.93, 2.20)</td>
</tr>
<tr>
<td>FIB-4 score</td>
<td>&lt;1.45</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>1.45-3.25</td>
<td>1.10 (0.68, 1.80)</td>
<td>1.27 (0.84, 1.93)</td>
</tr>
<tr>
<td>≥3.25</td>
<td><strong>2.25 (1.13, 4.47)</strong></td>
<td><strong>2.23 (1.26, 3.95)</strong></td>
</tr>
</tbody>
</table>

*Significant adjusted odds ratios are presented in bold.
Chapter 3:
Coinfection with Hepatitis C virus and/or Hepatitis B virus is associated with reduced survival among people living with HIV in early and later antiretroviral treatment eras
Abstract

Background  Hepatitis B and hepatitis C co-infection has been associated with increased mortality among people living with HIV. However, few studies have reported cause-specific mortality, so it is unclear as to whether increased mortality rates can be attributed to liver disease alone.

Methods  Within the Johns Hopkins Hospital HIV cohort, all-cause mortality rates of HIV mono-infected patients were compared to mortality rates of HIV/HBV coinfected, HIV/HCV coinfected, and HIV/HBV/HCV triply infected patients in the early ART era (1996-2001) and later ART era (2002-2013). The later ART era was marked by the introduction of HBV-active ART, pegylated interferon treatment for HCV, and more efficacious antiretrovirals for HIV. Cause-specific mortality was also described for each infection group in the early and modern ART eras. Poisson regression was used to evaluate factors associated with all-cause mortality.

Results  HIV mono-infected patients experienced significant declines in mortality in the later ART era compared to the early ART era [31.87 per 1000 PY (95%CI 28.86-35.18) vs. 50.62 per 1000 PY (95% CI 42.87-59.78) vs]. However, even after controlling for known factors of mortality such as age, CD4 count, and rates of viral suppression, HIV/HBV (IRR 1.74, 95% CI 1.33-1.29), HIV/HCV (IRR 1.3, 95% CI 1.14-1.49), and HIV/HBV/HCV triply infected (IRR 1.39, 95% CI 1.03-1.88) patients had significantly higher mortality when compared to HIV mono-infected patients in the second ART era. The percentage of deaths attributed to liver mortality in HIV/HBV coinfected patients did not change following the introduction of therapies for HBV.
(tenofovir). Additionally, the percentage of deaths attributed to liver mortality increased among HIV/HCV and HIV/HBV/HCV patients despite the introduction of pegylated-interferon.

**Conclusion** Co-infection with HBV, HCV, or both was associated with increased mortality compared to HIV mono-infected patients despite the introduction of more efficacious antiretrovirals for HIV, HBV-active therapy (tenofovir), and HCV therapy (pegylated-interferon).
Introduction

Combination antiretroviral therapy (cART) has drastically reduced HIV-related morbidity and mortality for HIV-infected individuals globally (134, 135). However, chronic diseases, including co-infection with hepatitis B or hepatitis C, have subsequently contributed to increasing liver-related morbidity and mortality in those living with HIV globally (134, 136).

Because HBV, HCV, and HIV have shared routes of transmission, co-infection may be common, especially in certain key populations such as injecting drug users. In North America, 55.2% (40.8-67.7) of PWID are estimated to be infected with HCV; in a national injecting drug user cohort drawing from Baltimore, Los Angeles, New York, and Chicago, the prevalence had decreased from 65% in 1994-1996 to 35% in 2002-2004 (137). Estimates may differ based on population sampled. In a separate Baltimore-based study of injecting drug users from a similar time period (2001-2004), the HCV prevalence rate was 69%. HCV prevalence is strongly associated with duration of injection; in the Baltimore-based study, African-Americans who had injected for more than five years being 13 times more likely to be HCV positive than those who had injected for less than one year (7). While HIV/HBV/HCV triple infection is also associated with injecting drug use, HIV/HBV coinfection is more likely to be seen in MSM in the US, and among those born outside North America due to the high prevalence of HBV in Asia, and parts of Africa (138-140).

Multiple studies have shown HBV and HCV individuals co-infected with HIV suffer from accelerated rates of liver disease, with faster progression to fibrosis, cirrhosis, and hepatocellular carcinoma (106). Additionally, they have higher rates of liver-related mortality.
compared to HIV mono-infected individuals alone (135, 141). In the US, mortality rates from liver disease caused by hepatitis C (HCV) surpassed mortality due to HIV in 2007, and HBV and/or HIV coinfection were independently associated with increased risk for HCV-related mortality (142). Co-infection with HBV among HIV infected individuals has also been associated with increased all-cause and liver-related mortality compared to mono-infected patients alone (143, 144). In the era of effective cART, HBV and/or HCV coinfection has not been shown to increase the rate of HIV progression to AIDS (141, 145, 146). However, it is unclear whether coinfection impacts mortality. While some multivariable analyses have demonstrated that the association between increased mortality for both HIV/HCV and HIV/HBV coinfected patients disappears after controlling for CD4 count or rates of HIV viral suppression, suggesting that treatment of HIV and immune reconstitution can level the playing field for coinfected patients, others have documented an increased risk of death for coinfected patients despite cART (147-150).

The purpose of this analysis was to 1) compare all-cause mortality rates and 2) examine cause-specific mortality for HIV/HBV, HIV/HCV, and HIV/HBV/HCV triply infected patients compared to HIV mono-infected patients at the Johns Hopkins HIV Clinic. For each group of patients, we hypothesized that 1) Mortality would decrease in the second era among HIV mono-infected patients with introduction of more effective antiretroviral therapies, including tenofovir and integrase inhibitors. 2) Among HIV/HBV coinfected patients, we hypothesized that the introduction of tenofovir, or HBV-active antiretroviral therapy, would decrease mortality among HIV/HBV coinfected patients, as there was previously no effective and durable
therapy for HBV. 3) For HIV/HCV coinfected patients, we hypothesized that mortality would be similar despite the introduction of more efficacious antiretroviral therapy for HIV and pegylated interferon for HCV treatment. This is because that while HIV-related mortality should decrease, HIV/HCV coinfected patients could subsequently experience increased liver mortality secondary to HCV due to low uptake and efficacy of HCV treatment in the pre-DAA era. While pegylated interferon was approved in 2002, the cutoff for this analysis occurred prior to the approval of sofosbuvir. Therefore, the second era (2002-2013) is a post pegylated-IFN, pre-DAA era. Additionally, as HIV/HCV coinfection is a surrogate marker of former or ongoing injecting drug use, substance use related deaths were not expected to decrease secondary to changes in antiretroviral treatment.

**Methods**

This analysis utilized prospective cohort data obtained through clinical practice at the Johns Hopkins HIV Clinic in Baltimore, Maryland. All patients enrolled at the Johns Hopkins HIV Clinic between January 1996 and March 2013 with known HBV or HCV status were included in the analysis. HBV infection was defined as any positive hepatitis B surface antigen (HbsAg) recorded in the medical record. HCV infection was defined as either reactive HCV antibody or a detectable HCV RNA. Patients without HBV or HCV data were assumed to be negative for both viruses and included as HIV mono-infected patients.

The primary objective of the analysis was to determine the impact of HBV and HCV co-infection on all-cause mortality by comparing mortality rates of HIV mono-infected, HIV/HBV coinfected, HIV/HCV coinfected, and HIV/HBV/HCV triply infected patients.
For HIV, we examine mortality in the early ART (1996-2001) and later ART (2002-2013) era. The first protease inhibitor, lopinavir/ritonavir, was approved by the US FDA in 2000. For HBV-coinfected patients, the eras correspond to when tenofovir, the first dually active HBV/HIV medication, was approved in 2001, or the pre-tenofovir (1996-2001) and post-tenofovir (2002-2013) eras. For HCV-coinfected patients, these eras also correspond to the approval of pegylated interferon in 2002, with a pre-peg-IFN era (1996-2001) and peg-IFN/pre-DAA era (2002-2013).

Data on mortality was obtained from the National Death Index (NDI Plus) and medical record review. Poisson regression was used to compare all-cause mortality rates by infection status. Participants entered the analysis on their date of enrollment into the cohort and exited on the date of death, last follow-up visit, or June 30, 2013. Time-fixed confounders considered for inclusion in the analysis included age at entry into the cohort, sex, and self-identified race. Time-varying confounders considered for inclusion in the analysis included ART, CD4 count, and HIV viral load. For participants with missing HIV viral load at clinic visits, the last available measure was carried forward (10.1% of clinic visits). An undetectable viral load was considered to be less than 400 copies/mL given changes in the lower limit of detection for HIV RNA tests during this time period. The analysis was conducted for the entire study period (1996-2013) and separately by treatment era.

For participants with HBV infection, the effect of tenofovir (TDF) on all-cause mortality in the modern treatment era (2002-2013) was also evaluated. Both HIV/HBV and HIV/HBV/HCV patients were combined into one category for this analysis. Tenofovir exposure was modeled in
two ways: 1) as a time-varying binary variable (either taking tenofovir or not at each clinic visit), or 2) as the cumulative time of exposure to tenofovir at each clinic visit. In the first case, because tenofovir is only administered as part of an antiretroviral treatment regimen, a new variable was constructed where patients were categorized as either 1) Off ART/off TDF, 2) On ART/off TDF, or 3) On ART/on TDF.

A secondary objective was to explore cause-specific mortality by categorizing all deaths based on primary cause of death. Cause of death was largely abstracted from National Death Index Plus (71% of all deaths) with the remainder done through medical record review. Categories of death included HIV-related, liver-related, cardiovascular-related, renal-related, pulmonary-related, malignancy, substance use, accidental, sepsis, or other (not falling into any of the other categories and unknown).

Results

In Table 1, summary characteristics at the time of enrollment to the HIV clinic by infection status in pre-tenofovir era (1996-2001) and post-tenofovir era (2002-2013) are presented. From 1996-2001, HIV (45.0%) and HIV/HCV (44.9%) coinfected patients made up the vast majority of clinic patients, with HIV/HBV (5.3%) and HIV/HBV/HCV (4.5%) patients making up a small proportion of total clinic patients. HIV mono-infected patients enrolled at median age of 36 years, compared to 39 years for HIV/HCV and HIV/HBV/HCV; 69% of HIV mono-infected patients were black, and 33% were female. While 50% of HIV mono-infected patients reported heterosexual risk for HIV acquisition and 39.9% reported being MSM, the majority of HIV/HCV (79.6%) and HIV/HBV/HCV (78.4%) patients reported IVDU. The median CD4 count at
presentation was greater than 200 but less than 300 for all groups. ART use was highest among mono-infected (35.4%) and HIV/HBV (41.7%) coinfected patients, but still low overall. Subsequently, rates of HIV suppression were less than 20% for all groups of patients.

In the post-tenofovir era (2002-2013), HIV mono-infected patients comprised a larger percentage of the overall clinic population (51.9%), followed by HIV/HCV (40.3%), HIV/HBV (4.7%), and HIV/HBV/HCV (3.2%) triply infected patients. IVDU continued to make up a small percentage of the HIV mono-infected group (5.4%), but still represented large proportions of HIV/HCV (74.8%) and HIV/HBV/HCV (73.3%) groups. The median age of presentation at time of enrollment rose for all groups. Gender and race distribution did not differ between the two eras aside from more females (22% vs. 5.8% previously) being HIV/HBV coinfected. Median CD4 rose across all groups, and over half of all groups were on ART. Although rates of HIV suppression increased in the post-tenofovir era, they still remained below 35% for all groups; notably, HIV/HBV/HCV patients had the lowest rate of viral suppression at 23%.

Mortality rates by infection status in both eras are presented in Table 2. In the pre-tenofovir, pre-peg-IFN era (1996-2002), HIV/HBV/HCV patients had the highest mortality rate at 93 (95% CI 63.34-136.62) per 1000 PY followed by HIV/HBV patients at 70.68 (95% CI 46.54-107.34) per 1000 PY, HIV/HCV patients at 59.46 (51.28-68.96) per 1000 PY, and HIV mono-infected patients at 50.62 (42.87-59.78) per 1000 PY. In the post-tenofovir and peg-IFN era (2002-2013), mortality rates decreased for all groups; however, the most substantial decreases were seen in HIV/HBV/HCV triply infected, where mortality decreased to 60.95 (95% CI 45.93-80.87) per 1000 PY, and HIV mono-infected, where mortality decreased to 31.87 (95% CI 28.86-
While HIV/HBV and HIV/HCV coinfected patients also experienced decreased mortality rates in the post-tenofovir era, they were not as substantial, and the 95% confidence intervals for mortality between the pre- and post-tenofovir eras for these two groups were largely overlapping (Figure 1). Additionally, in the post-tenofovir era; due to the large decrease in mortality for HIV mono-infected, all groups had significantly higher IRR for mortality compared to HIV mono-infected alone: HIV/HBV patients and HIV/HBV/HCV patients had the highest crude IRRs at 1.9, followed by HIV/HCV at 1.73. The increasing disparity in mortality in the later ART era is depicted in Kaplan-Meier curves comparing survival among HIV mono-infected vs. HIV/HBV, HIV/HCV, and HIV/HBV/HCV coinfected patients; in the second panel encompassing both ART eras, the survival curves for all coinfected groups diverge from that of HIV mono-infected patients (Figure 2).

Primary cause of death by era and infection status is presented in Table 3. Despite a significant decrease in mortality rate between early ART and later ART (post-tenofovir and protease inhibitors) among HIV mono-infected patients, HIV remained the primary cause of death for this group, representing 30.9% of all deaths in both eras. For coinfected patients, HIV-related mortality also remained the primary cause of death for all groups in both eras, with the share of deaths attributed to HIV actually increasing in all groups. In the modern ART era, HIV deaths represented 28.3% of deaths in HIV/HBV coinfected, 21.5% in HIV/HCV coinfected, and 22.9% in HIV/HBV/HCV coinfected.

Liver deaths were more common in all groups of coinfected patients compared to HIV mono-infected patients. Furthermore, the percentage of deaths attributed to liver-related
causes increased across all infection status groups in the post-tenofovir, post-peg-IFN era. From 2002-2013, liver deaths represented 10% of HIV/HBV deaths, 8.4% of HIV/HCV deaths, and 12.5% of HIV/HBV/HCV deaths. For HIV mono-infected patients, during the same time period, only 3.3% of deaths were attributed to liver-related mortality.

One notable cause of death in all groups was septicemia. HIV/HBV coinfected patients had the highest septicemia-related mortality both pre- (18.2%) and post-tenofovir (16.7%). For HIV/HCV, the percentage of deaths attributed to septicemia was stable at close to 14% for both eras, and for HIV/HBV/HCV patients, septicemia deaths were 15.4% and 10.4% in the pre-tenofovir and post-tenofovir eras. Septicemia deaths increased in HIV mono-infected patients in the post-tenofovir era to 9.4% compared to 5.8% in the early ART era, but remained less than all other co-infected patients. Finally, substance use was listed as the primary cause of death for 9.9% of deaths in HIV/HCV coinfected, and 6.3% of deaths in HIV/HBV/HCV coinfected patients; many of these were directly related to injecting drugs and/or overdose.

To explore covariates associated with increased mortality, Poisson regression was used to model the effect of various factors on mortality. When controlling for gender, race, age, CD4 count, and viral suppression, all groups of coinfected patients had higher IRRs compared to mono-infected patients (Table 5). HIV/HBV had the highest mortality (IRR 1.74, 95% CI 1.33-2.29), followed by HIV/HBV/HCV (IRR 1.39, 95% CI 1.03-1.88), and HIV/HCV (IRR 1.3, 95% CI 1.14-1.49). Other factors that were associated with mortality in this model included increasing age and less time spent virally suppressed. For those who had 0-25% of their visits with a recorded HIV RNA > 400, the IRR for mortality was 2.35 higher than those who had >75% of
their visits with undetectable viral loads. Higher CD4 counts were associated with lower mortality. In this model, female gender and black race did not have an impact on mortality.

Finally, for HIV/HBV patients, we examined whether the introduction of tenofovir, or HBV-active ART, would impact mortality. Both HIV/HBV and HIV/HBV/HCV patients enrolled in the post-tenofovir era were included in this analysis. First, time-varying tenofovir as a single predictor in Poisson regression was examined. This yielded an IRR of 0.42 (95% CI 0.27-0.63), indicating those who were on tenofovir had decreased mortality compared to those who were not. To examine the effect of cumulative tenofovir, time-varying cumulative tenofovir (per year increase in cumulative tenofovir use) was calculated, and yielded an IRR of 0.83 (95% CI 0.74-0.92), indicating that for every additional year of tenofovir that an HIV/HBV coinfected patient took, the incidence of mortality decreased by 17%. In Table 5, a model is presented examining the effect of tenofovir as part of a combined antiretroviral regimen. In this model, both patients who were on ART without tenofovir as well as those who were on a tenofovir-containing regimen had significantly decreased mortality compared to those not on ART. While the patients on tenofovir-containing ART had slightly decreased mortality (IRR 0.31) compared to those on ART without tenofovir (IRR 0.44) after controlling for age and CD4 count, the confidence intervals for both overlapped with each other, indicating that there was not a statistically significant difference between them.

Discussion

Although advances in antiretroviral therapy between the early and modern ART era drastically reduced mortality among HIV mono-infected patients, co-infection with HBV, HCV,
or both was associated with increased mortality even after adjustment for other known predictors of mortality such as age, CD4 count, and rates of viral suppression. The introduction of HBV-active HAART and pegylated interferon did not impact all-cause mortality for HIV/HBV and HIV/HCV coinfected patients, with crude mortality rates for both groups remaining almost identical in the early and modern ART eras.

HIV/HBV coinfected patients had the highest risk of mortality compared to HIV mono-infected patients in our analysis. Despite the introduction of tenofovir, the IRR for all-cause mortality among HIV/HBV coinfected patients did not significantly change in the pre-tenofovir (70.68 per 1000 PY, 95% CI 46.5-107.34) era compared to the post-tenofovir (60.84 per 1000 PY, 95% CI 47.24-78.35) era. In the post-tenofovir era, HIV/HBV coinfected patients were 1.74 times more likely to die compared to HIV mono-infected patients after adjustment for other known predictors of mortality. This is consistent with other HIV cohorts based in Europe, where HIV/HBV coinfected patients were 1.6 or 1.54 times likely to die compared to HIV mono-infected patients(151, 152). These two cohorts, as well as the MACS cohort, demonstrated the increased risk of liver-related mortality among HIV/HBV coinfected patients compared to HIV mono-infected patients(153). In a cohort study from the United Kingdom, compared to HIV mono-infected patients, HIV/HBV coinfected patients had an adjusted IRR of 10.42 for liver-related mortality and HIV/HBV/HCV triply infected patients had an adjusted IRR of 15.19(151).

While HIV/HBV patients did experience more liver-related deaths when compared to HIV mono-infected patients, the percentage of liver deaths among HIV/HBV coinfected patients did not decrease in the pre-tenofovir (8.3%) vs. post-tenofovir (11.1%) era, indicating that HBV-
active antiretroviral therapy with tenofovir did not make a significant difference in the risk of death when compared to antiretroviral therapy alone. One potential cause for increased mortality among HIV/HBV patients in our analysis is higher rates of immunosuppression, as HIV/HBV patients presented for care at lower baseline CD4 counts than all other groups in both the pre- and post-tenofovir era. Lower CD4 counts at presentation among HIV/HBV patients have been reported in other cohorts, and has been inversely associated with liver fibrosis in some, but not all studies (154). In the MACS cohort, having chronic hepatitis B carried a higher risk of death from liver disease than chronic hepatitis C. Among HIV infected subjects, CD4<200 was associated with a 16.2 fold increased risk of liver related death compared with those who had CD4 counts >350 (155). In a Canadian cohort of HIV/HBV coinfected patients, there was no association between low CD4 T cell counts and fibrosis defined as APRI>=1.5 at time of ART initiation. However, low baseline CD4 count was associated with fibrosis at end of follow up (139). Interestingly, post-ART fibrosis scores improved most among HIV/HBV coinfected participants; at a median follow up time of 5.97 years, HBV coinfection was no longer independently associated with fibrosis. While this is consistent with other cohorts that demonstrate reduction in liver fibrosis with the use of HBV-active ART, it is unclear if this reduction translates into reduction in liver-related or all-cause mortality (156, 157). In our cohort, the introduction of tenofovir did not reduce liver-related or all-cause mortality.

One strength of our analysis is the exploration of cause-specific mortality. Other studies have explored liver, AIDS-related, or all-cause mortality among coinfected patients but do not specifically explore other causes of mortality. In our cohort, deaths secondary to septicemia
represented a higher percentage of deaths as compared to liver-related deaths in HIV/HBV patients as well as HIV/HCV coinfected patients in the modern ART era. Additionally, all groups of coinfected patients had higher rates of septicemia mortality when compared to HIV mono-infected patients, suggesting that coinfection may predispose or contribute to worse outcomes during hospitalizations due to or leading to sepsis. Notably, HBV-coinfected patients were also more likely to be HCV coinfected. Of those with HIV/HBV coinfection, 40.3% were also coinfected with HCV in the post-tenofovir era; in contrast, for those with HIV/HCV coinfection, only 7.9% were coinfected with HBV.

In a 2011 analysis utilizing inpatient hospitalizations in the US comparing HIV mono-infected, HBV mono-infected, and HIV/HBV coinfected patients, HIV/HBV and HIV mono-infected patients had similar rates of hospitalization for infections, including septicemia. However, HIV/HBV coinfection was associated with higher in-hospital mortality from all causes compared to HIV mono-infected patients (OR 3.00, 95% CI 1.8-5.02) in those with cirrhosis or portal hypertension. In addition, length of stay in HIV/HBV coinfected and rates of hospitalization were higher when compared to HIV and HBV mono-infected patients(158). In another analysis of hospitalizations in the HIV Research Network, all groups of coinfected patients had higher rates of hospitalizations for non-AIDS-defining infections when compared to HIV mono-infected patients alone. HIV/HBV and HIV/HBV/HCV triply infected patients had the highest percentages of admissions for sepsis/bacteremia in this category, with nearly a quarter of all hospitalizations being related to sepsis/bacteremia for both of these infection status categories(159).
The introduction of pegylated interferon for the treatment of HCV did not impact mortality among HIV/HCV coinfected patients, as crude mortality rates remained essentially unchanged in the pre- (59.46 per 1000 PY, 95% CI 51.28-68.96) and post-pegylated interferon (55.09 per 1000 PY, 95% CI 50.7-59.86) eras. This is unsurprising given the low uptake of interferon-based therapy for HCV and the suboptimal cure rates during that time. In the Hopkins Clinic population, only 208 HIV/HCV coinfected patients, or 11.2% of patients with HCV in the clinic had initiated treatment with an interferon-containing regimen between 1996 and 2013. Of those, only 17% were cured.

After controlling for CD4 count, age, and HIV RNA suppression, HIV/HCV patients had increased mortality compared to HIV mono-infected patients (IRR 1.3), which was similar to triply infected patients in the post-tenofovir, post-peg-IFN era (IRR 1.39). Both HIV/HCV and HIV/HBV/HCV coinfected patients were more likely to report IVDU as a risk factor for HIV acquisition. Although we did not analyze data related to other forms or methods of drug use aside from IVDU, those with HIV/HCV coinfection were more likely to have substance use listed as their primary cause of death compared to HIV mono-infected patients, and had more deaths attributed to substance use than those attributed to liver-related mortality (55 deaths vs. 47 deaths) in the modern ART era. This underscores the need to provide access to treatment for both addiction and overdose prevention in these vulnerable populations.

Antiretroviral treatment significantly reduced mortality among HIV mono-infected patients in the Johns Hopkins HIV Clinic Cohort in the early vs. later ART eras, with mortality decreasing from 50.62 per 1000 PY (95% CI 42.87-59.78) from 1996-2001 to 31.87 per 1000 PY
(95%CI 28.86-35.18) in 2002-2013. However, the percentages of deaths attributed to HIV in the early and later ART eras among HIV mono-infected patients remained unchanged at 30.9%. HIV also remained one of the leading causes of death for all coinfected groups in both eras. Lack of viral suppression was one of the strongest predictors of death in the later ART era (2002-2013), with those who had 0-25% of their recorded HIV RNA levels <400 at highest risk of death (IRR 2.35, 95% CI 1.92-2.87). This analysis did not formally explore factors related to the HIV care cascade. However, delays in HIV diagnosis and presentation to care at low CD4 counts as well as inability to maintain consistent HIV viral suppression underscore the need to address larger systemic factors in access to testing and care to prevent HIV-related morbidity and mortality.

There are limitations to this study. First, there may be a survival bias as patients who were diagnosed with HIV and enrolled in care during the early ART era (1996-2001) but survived to the modern ART era (2002-2013) were included in the analysis for both eras. Second, as we categorized all patients with HCV antibody as being HIV/HCV coinfected, we may be overestimating HIV/HCV prevalence, as some did not have HCV RNA available. Finally, information regarding mortality and its causes were largely obtained from the National Death Index, and were not verified from other sources (such as the Social Security Death Master File); this could have caused an underreporting of number of deaths(160). Where primary cause of death was unavailable through NDI plus, medical record review was attempted, and 20.4% of deaths had medical record review by a single person to try and ascertain primary cause of death. Despite this, it was still not possible to ascertain cause of death for 25% of the deaths in the early ART era (1996-2001) and 6.24% of deaths in the later ART era (2002-2013). Finally,
this cohort is drawn from a single urban academic center in the United States with most patients being black. While other non-US cohorts may have differing demographic characteristics and therefore make our findings less generalizable to their populations, race did not have an effect on mortality in any of our analyses.

In conclusion, despite advances in antiretroviral therapy for HIV, patients coinfected with HBV, HCV, or both continued to have significantly increased mortality compared to HIV mono-infected patients alone. This was largely driven by a reduction in mortality for HIV mono-infected patients. Although coinfected patients had higher liver-related mortality compared to mono-infected patients in both eras, the proportion of liver-related deaths did not change for HIV/HBV coinfected patients following the introduction of tenofovir, or HBV-active antiretroviral therapy. Further research is needed to investigate whether length of HBV DNA viral suppression (or time on tenofovir) impacts liver mortality for HIV/HBV coinfected patients. For HIV/HCV coinfected patients, a key question in the post-DAA era is whether curative HCV treatment impacts both liver and all-cause mortality. In our analysis, other causes of mortality—including those related to substance use—represented a higher percentage of deaths compared to liver related mortality. Without addressing underlying structural barriers to provide addiction treatment and comprehensive harm reduction to these PWID, it is unlikely that we can make meaningful progress in reducing mortality among this vulnerable population.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HIV</th>
<th>HIV/HBV</th>
<th>HIV/HCV</th>
<th>HIV/HBV/HCV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Era 1</strong> (n=1118)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Era 2</strong> (n=2213)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Era 1</strong> (n=120)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Era 2</strong> (n=200)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Era 1</strong> (n=1100)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Era 2</strong> (n=1718)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Era 1</strong> (n=111)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Era 2</strong> (n=135)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Median age (IQR)</strong></td>
<td>36 (31-42)</td>
<td>39 (32-46)</td>
<td>35 (32-40)</td>
<td>39 (34-49)</td>
</tr>
<tr>
<td><strong>Female gender</strong></td>
<td>367 (32.8%)</td>
<td>793 (35.8%)</td>
<td>19 (15.8%)</td>
<td>375 (34.1%)</td>
</tr>
<tr>
<td><strong>Black</strong></td>
<td>774 (69.2%)</td>
<td>1577 (71.3%)</td>
<td>85 (70.8%)</td>
<td>920 (83.6%)</td>
</tr>
<tr>
<td><strong>Self-reported risk category</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVDU</td>
<td>80 (7.2%)</td>
<td>119 (5.4%)</td>
<td>14 (11.7%)</td>
<td>1285 (74.8%)</td>
</tr>
<tr>
<td>MSM</td>
<td>446 (39.9%)</td>
<td>819 (37.0%)</td>
<td>67 (55.8%)</td>
<td>861 (50.1%)</td>
</tr>
<tr>
<td>Heterosexual</td>
<td>565 (50.5%)</td>
<td>1207 (54.5%)</td>
<td>43 (35.8%)</td>
<td>541 (49.2%)</td>
</tr>
<tr>
<td><strong>CD4 count: Median (IQR)</strong></td>
<td>237 (65-454)</td>
<td>321 (152,502)</td>
<td>137(43-357)</td>
<td>301 (136-504)</td>
</tr>
<tr>
<td>&lt;200</td>
<td>502 (45.1%)</td>
<td>692 (31.3%)</td>
<td>69(57.5%)</td>
<td>424 (38.8%)</td>
</tr>
<tr>
<td>200-349</td>
<td>496 (22.4%)</td>
<td>496 (20.1%)</td>
<td>39 (19.5%)</td>
<td>409 (23.8%)</td>
</tr>
<tr>
<td>350+</td>
<td>400 (35.9%)</td>
<td>1025 (46.3%)</td>
<td>31 (25.9%)</td>
<td>414 (37.9%)</td>
</tr>
<tr>
<td>On ART</td>
<td>396 (35.4%)</td>
<td>1141 (51.6%)</td>
<td>50 (41.7%)</td>
<td>888 (51.7%)</td>
</tr>
<tr>
<td>HIV RNA&lt;400</td>
<td>173 (16.1%)</td>
<td>728 (32.9%)</td>
<td>21(18.1%)</td>
<td>15 (14.2%)</td>
</tr>
</tbody>
</table>

For self-reported risk category, patients could report more than one category of risk. Total number of patients included in Era 1 was 2449; Total patients in Era 2 was 4266. Era 1 encompassed the time period of 1996-2001, prior to the introduction of tenofovir and pegylated-interferon. Era 2 encompassed the years 2002-2013, when integrase inhibitors, tenofovir, and pegylated interferon were available.

Abbreviations: IVDU, intravenous drug use, MSM, men who have sex with men, ART, antiretroviral therapy
<table>
<thead>
<tr>
<th>Infection Status</th>
<th>Number of Deaths</th>
<th>Era 1</th>
<th>Era 2</th>
<th>Incidence Rate per 1000 PY (95% CI)</th>
<th>Era 1</th>
<th>Era 2</th>
<th>Crude IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>139</td>
<td>392</td>
<td></td>
<td>50.62 (42.87-59.78)</td>
<td></td>
<td></td>
<td>REF</td>
</tr>
<tr>
<td>HIV/HBV</td>
<td>22</td>
<td>60</td>
<td></td>
<td>70.68 (46.54-107.34)</td>
<td></td>
<td></td>
<td>1.39 (0.89-2.19)</td>
</tr>
<tr>
<td>HIV/HCV</td>
<td>175</td>
<td>558</td>
<td></td>
<td>59.46 (51.28-68.96)</td>
<td></td>
<td></td>
<td>1.17 (0.94-1.47)</td>
</tr>
<tr>
<td>HIV/HBV/HCV</td>
<td>26</td>
<td>48</td>
<td></td>
<td>93.02 (63.34-136.62)</td>
<td></td>
<td></td>
<td>1.84 (1.21-2.79)</td>
</tr>
</tbody>
</table>

Total number of patients included in Era 1 was 2449; Total patients in Era 2 was 4266.
Figure 3-1: Crude all-cause mortality rates by infection status and era

Note: Crude data from this figure was obtained from Table 3-2 (above). Era 1 is shown in blue on the left and Era 2 is shown in red on the right for each infection status.
**Figure 3-2 (Panels A, B): Kaplan-Meier Survival Curves by Infection Status and Era**

In the figures below, each survival curve represents patients in each infection status: HIV mono-infected patients (blue), HIV/HBV coinfected patients (brown), HIV/HCV coinfected patients (green), and HIV/HBV/HCV triply infected patients (orange).

**Panel A: KM Survival Curve by Infection Status, Early ART era (1996-2001).**

![Panel A](image)

Log-rank test: \(p=0.02\)

**Panel B: KM Survival Curve by Infection Status, Early and Later ART eras (1996-2013).**

![Panel B](image)

Log-rank test: \(p<0.0001\)
### Table 3-3: Primary Cause of Death by Infection Status in Early and Later ART Periods

<table>
<thead>
<tr>
<th>Time period (number of deaths)</th>
<th>Era 1 (n=139)</th>
<th>Era 2 (n=392)</th>
<th>Era 1 (n=22)</th>
<th>Era 2 (n=60)</th>
<th>Era 1 (n=175)</th>
<th>Era 2 (n=558)</th>
<th>Era 1 (n=26)</th>
<th>Era 2 (n=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cause of death (percentage of deaths by infection status)</strong></td>
<td>HIV</td>
<td>HIV/HBV</td>
<td>HIV/HCV</td>
<td>HIV/HBV/HCV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver (percentage of deaths by infection status)</td>
<td>0 (0%)</td>
<td>2 (9.1%)</td>
<td>9 (5.1%)</td>
<td>2 (7.7%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td>43 (30.9%)</td>
<td>121 (30.9%)</td>
<td>4 (18.2%)</td>
<td>17 (28.3%)</td>
<td>30 (17.1%)</td>
<td>120 (21.5%)</td>
<td>5 (19.2%)</td>
<td>11 (22.9%)</td>
</tr>
<tr>
<td>Substance use</td>
<td>2 (1.4%)</td>
<td>0 (0%)</td>
<td>11 (6.3%)</td>
<td>5 (3.8%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accidents, MVA, violence</td>
<td>2 (1.4%)</td>
<td>1 (0.4%)</td>
<td>3 (1.7%)</td>
<td>0 (0%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular and cardiovascular disease</td>
<td>9 (6.5%)</td>
<td>63 (16.0%)</td>
<td>2 (9.1%)</td>
<td>9 (15%)</td>
<td>12 (6.9%)</td>
<td>64 (11.5%)</td>
<td>0 (0%)</td>
<td>8 (16.7%)</td>
</tr>
<tr>
<td>Lung (COPD, pneumonia, flu)</td>
<td>10 (7.2%)</td>
<td>38 (9.7%)</td>
<td>2 (9.1%)</td>
<td>4 (6.7%)</td>
<td>14 (8.0%)</td>
<td>39 (7.0%)</td>
<td>1 (3.8%)</td>
<td>3 (6.3%)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>12 (8.6%)</td>
<td>29 (7.4%)</td>
<td>3 (13.6%)</td>
<td>6 (10%)</td>
<td>9 (5.1%)</td>
<td>29 (5.2%)</td>
<td>1 (3.8%)</td>
<td>3 (6.3%)</td>
</tr>
<tr>
<td>Renal disease</td>
<td>1 (0.7%)</td>
<td>5 (1.3%)</td>
<td>0 (0%)</td>
<td>3 (5.0%)</td>
<td>2 (1.1%)</td>
<td>16 (2.9%)</td>
<td>1 (3.8%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Septicemia</td>
<td>8 (5.8%)</td>
<td>37 (9.4%)</td>
<td>4 (18.2%)</td>
<td>10 (16.7%)</td>
<td>24 (13.7%)</td>
<td>77 (13.8%)</td>
<td>4 (15.4%)</td>
<td>5 (10.4%)</td>
</tr>
<tr>
<td>Other</td>
<td>13 (9.4%)</td>
<td>40 (10.2%)</td>
<td>2 (9.1%)</td>
<td>3 (5.0%)</td>
<td>17 (9.7%)</td>
<td>56 (10.0%)</td>
<td>4 (15.4%)</td>
<td>8 (16.7%)</td>
</tr>
<tr>
<td>Unknown (percentage of deaths by infection status)</td>
<td>39 (28.1%)</td>
<td>24 (6.1%)</td>
<td>2 (9.1%)</td>
<td>1 (1.7%)</td>
<td>43 (24.6%)</td>
<td>40 (7.2%)</td>
<td>7 (26.9%)</td>
<td>1 (2.1%)</td>
</tr>
</tbody>
</table>
### TABLE 3-4: INCIDENCE RATE RATIOS OF MORTALITY BY COVARIATE IN LATER ART ERA (2002-2013).

<table>
<thead>
<tr>
<th>Incidence rate ratio</th>
<th>(95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>0.97 (0.85-1.1)</td>
<td>0.66</td>
</tr>
<tr>
<td>Black</td>
<td>1.09 (0.93-1.23)</td>
<td>0.28</td>
</tr>
<tr>
<td><strong>Coinfection status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV mono-infection</td>
<td>REF</td>
<td></td>
</tr>
<tr>
<td>HIV/HBV</td>
<td>1.74 (1.33-2.29)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HIV/HCV</td>
<td>1.3 (1.14-1.49)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HIV/HBV/HCV</td>
<td>1.39 (1.03-1.88)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td>REF</td>
<td></td>
</tr>
<tr>
<td>40-44</td>
<td>1.34 (1.14-1.57)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>45-49</td>
<td>1.38 (1.15-1.65)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;50</td>
<td>1.71 (1.43-2.05)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>CD4 count</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;200</td>
<td>REF</td>
<td></td>
</tr>
<tr>
<td>200-349</td>
<td>0.38 (0.33-0.45)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>350+</td>
<td>0.19 (0.17-0.23)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>HIV RNA&lt;400 (% of total visits)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;75</td>
<td>REF</td>
<td></td>
</tr>
<tr>
<td>26-75</td>
<td>1.43 (1.16-1.75)</td>
<td>0.001</td>
</tr>
<tr>
<td>0-25</td>
<td>2.35 (1.92-2.87)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
### Table 3-5: Incidence Rate Ratios for Mortality for All HIV Patients Coinfected with HBV in the Post-TDF Era (2002-2013).

<table>
<thead>
<tr>
<th></th>
<th>Incidence rate ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Female</strong></td>
<td>0.74 (0.45-1.24)</td>
<td>0.26</td>
</tr>
<tr>
<td><strong>Black</strong></td>
<td>0.89 (0.55-1.42)</td>
<td>0.61</td>
</tr>
<tr>
<td><strong>IVDU</strong></td>
<td>1.24 (0.83-1.86)</td>
<td>0.83</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td>REF</td>
<td></td>
</tr>
<tr>
<td>40-44</td>
<td>1.64 (1.02-2.64)</td>
<td>0.37</td>
</tr>
<tr>
<td>45-49</td>
<td>1.28 (0.74-2.19)</td>
<td>0.07</td>
</tr>
<tr>
<td>&gt;50</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CD4 count</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;200</td>
<td>REF</td>
<td></td>
</tr>
<tr>
<td>200-349</td>
<td>0.29 (0.17-0.49)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>350+</td>
<td>0.14 (0.09-0.24)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>ART/TDF status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No ART/No TDF</td>
<td>REF</td>
<td></td>
</tr>
<tr>
<td>ART/No TDF</td>
<td>0.44 (0.27-0.69)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ART/TDF</td>
<td>0.31 (0.19-0.48)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Abbreviations: IVDU, intravenous drug use; ART: antiretroviral therapy; TDF: tenofovir.
Chapter 4:
Group sex and methamphetamine use fuel an explosive epidemic of Hepatitis C among HIV-infected men who have sex with men in Bangkok, Thailand
Abstract

Background: Increased rates of hepatitis C virus (HCV) infection among HIV-infected men who have sex with men (MSM) and who deny injecting drugs have been reported in resource-rich settings.

Setting: We measured HCV prevalence and incidence in a predominantly MSM cohort with acute HIV infection (AHI) in Bangkok, Thailand.

Methods: In 2009-2018, participants with AHI were enrolled into the SEARCH010/RV254 cohort. HCV antibody was measured at enrollment and at least once annually. Infection was confirmed with HCV RNA. Risk factors for HCV were analyzed by proportional hazards regression, with hazard ratios (HR) calculated in a multivariable model.

Results: Of 573 participants, 94% were MSM, with median age of 26 years (range 18-70). Prevalence of HCV antibody was 9/573, or 1.6% (95% CI 0.7-3.0%). In 1883 person-years of follow up (PYFU), 39 incident cases were identified (20.7 per 1000PY ,95% CI 15.1-28.3). All incident cases were identified from 2014 onwards, and incidence rose from a range of 7.5-11.4 per 1000 PY between 2014-2016 to 44.8 per 1000PY in 2018 (p=0.001). Most cases (97.4%) were MSM, and denied injecting (37/39, 94.5%). In multivariate analysis, methamphetamine use (adjusted HR 2.33, 95% CI 1.13 -4.8, p=0.022), group sex (adjusted HR of 2.54 (95% CI 1.26-5.12, p=0.009), and history of positive TPHA/RPR (adjusted HR 2.43 (95% CI 1.22-4.85), p=0.012) were significantly associated with incident HCV.
Conclusion: We report an HCV epidemic among this cohort of HIV-infected Bangkok-based MSM. Access to timely HCV diagnosis and treatment is needed to prevent morbidity and decrease onward transmission.

Introduction

In resource-rich settings, sexually transmitted hepatitis C virus (HCV) infection among HIV-infected men who have sex with men (MSM) and who deny injecting drug use has emerged as an important comorbidity, with HCV epidemics among HIV-infected MSM described in the US and Europe(161, 162). Increased HCV incidence also has been documented in predominantly HIV-infected MSM cohorts in Taiwan, Hong Kong, and Japan, with dramatic increases in HCV incidence starting in 2006 and continuing through 2016 (163-165). However, there is very limited data on HCV prevalence and incidence among MSM in Southeast Asia, especially in low- and middle-income countries (LMIC).

Individuals with HIV/HCV coinfection have higher rates of morbidity and mortality when compared to mono-infection with either virus alone. Liver fibrosis progresses at an accelerated rate in co-infection when compared to HCV infection alone (166). Among HIV-infected patients, co-infection with HCV leads to an increased risk for liver decompensation, liver-related death, and increased all-cause mortality (167, 168). In addition, extrahepatic manifestations, including increased risk for cardiovascular, metabolic, and renal disease in those with HIV/HCV compared to HIV monoinfected individuals, can cause complications leading to non-liver related morbidity and mortality (169-171).
Although Thailand does have universal access to antiretroviral treatment (ART) for HIV through a national AIDS program, access to direct-acting antivirals (DAA)-based HCV treatment for HIV-infected individuals remains limited under the universal health care program (UHC). First, only patients who receive evaluation with transient elastography or a blood fibromarker panel and have fibrosis scores of F2 or higher are eligible for treatment. Second, as of March 2020, UHC formularies only carry sofosbuvir/ledipasvir. This combination is ineffective for genotype 3, which represents nearly half of all HCV infections in Thailand. For those covered under UHC, the 2018 Thai Guidelines for Management of Chronic Hepatitis C recommend that those with genotype 3 receive sofosbuvir, pegylated interferon, and ribavirin (172). Although generic sofosbuvir/velpatasvir was approved by the Thai FDA in August 2019, it has yet to be included in universal health care coverage pending price negotiations. Finally, prescription of DAAs have generally been restricted to liver specialists or certain infectious diseases physicians.

This study aimed to characterize the prevalence and incidence of HCV infection and elucidate risk factors for HCV acquisition among a predominantly MSM cohort of HIV-infected individuals who were identified during acute HIV infection (AHI) in Thailand.

**Methods**

The RV254/SEARCH010 (clinical trials.gov NCT00796146) enrolls adults diagnosed with AHI on presentation for HIV testing from Bangkok, Thailand since 2009. The majority of participants are diagnosed from the Thai Red Cross Anonymous Clinic located in Bangkok; 22 (3.8%) participants came from the RV217 cohort in Pattaya, Thailand (173). AHI was defined by either a nonreactive fourth-generation immunoassay with a positive nucleic acid test or reactive fourth-generation immunoassay with a nonreactive second-generation immunoassay.
Participants are offered immediate ART via a separate protocol (clinicaltrials.gov NCT00796263), and longitudinal follow-up for up to 14 years. Follow-up includes clinical, virological, and immunological testing at least every 12 weeks for the first two years, then every 12 to 24 weeks for the remainder of participation. Participants were included in this analysis if they enrolled in the cohort through October 31, 2018.

HCV antibody and hepatitis B (HBV) serology (anti-HBs, HBsAg, anti-HBc) were measured at enrollment and then annually in all participants. Screening for hepatitis A (HAV) antibody (anti-HAV IgG) was started in 2017 after an outbreak of acute HAV occurred in the cohort (175). Hepatitis serology could be repeated at any time point if clinically indicated. Participants without protective antibody to HAV or HBV were offered immunization. HCV prevalence at HIV diagnosis was determined by a positive HCV antibody test (ARCHITECT anti-HCV, Abbott, USA) at study enrollment. Incident HCV was defined as a confirmed positive HCV antibody test or HCV RNA (Abbott RealTime HCV) above the level of detection following at least one negative HCV antibody test. HCV genotyping (Abbott RealTime HCVgenotype II) was performed on those with detectable HCV RNA. Syphilis screening was conducted every six months using treponema pallidum haemagglutination (TPHA) with rapid plasma reagin (RPR) confirmation, but could be ordered more frequently if clinically indicated.

Substance use and sexual risk behavior was captured during patient interviews at each clinic visit, generally every 12 weeks, and also by semiannual confidential computer-assisted self-interview (CASI). Baseline data recorded substance use during the previous 4 months prior to HIV diagnosis. Subsequent visits recorded use over the previous 3 to 6 months, depending on
the frequency of study visits. Through 2014, recreational drug use data collected included inhaled alkyl nitrites (poppers), amphetamine, methamphetamine, heroin, cannabis, and non-prescribed use of erectile dysfunction medications. Alcohol use was recorded as yes or no. Starting in 2015, additional data was collected on use of opium, ketamine, Gamma Hydroxybutyrate (GHB), ecstasy, and quantification of alcohol use. Risky alcohol use was defined at an AUDIT-C score of > 4 for males and > 3 for females (176). Data on group sex, defined as a sexual encounter with 3 or more people including the participant within the previous 6 months, was collected systematically starting in 2017. When physician interview was discordant with the CASI, CASI data was used in the analysis as some participants may not want to report substance use to providers.

HCV prevalence rate at study enrolment by calendar year was calculated as the number of participants with HCV antibody positive at enrollment divided by total enrollment in the given year. Incidence density rates per year were calculated by dividing the number who seroconverted HCV antibody from negative to positive during the calendar year by the number of person years contributed by participants who were still at risk and active in the cohort study in the given year. Follow up time was censored upon seroconversion, study withdrawal, loss to follow-up, death or end of the year: 31 December for years 2009-2017 and 31 October for year 2018. A Poisson regression model was used to compare incidence rates by year. Risk factors for HCV acquisition were analyzed by proportional hazards regression, with hazard ratios (HR) calculated in univariate and multivariate models. For all analyses, a two-sided type I error less than 5% was considered statistically significant. Analyses were performed using GraphPad
Prism 7.00 (GraphPad Software, La Jolla, CA, USA) and Stata 15.0 (StataCorp LP, College Station, TX, USA).

All participants gave written informed consent. The study was approved by the institutional review boards at Chulalongkorn University in Thailand and at Walter Reed Army Institute of Research in the USA.

Results

All 573 participants who were enrolled into the RV254/SEARCH10 cohort through October 2018 were included in the analysis. As shown in Table 1, most baseline characteristics, including age, gender, sexual orientation, CD4 count, and HIV RNA level at time of HIV diagnosis did not significantly differ by HCV status. The median age at time of HIV diagnosis was 26 years (IQR 22-31) and 97.4% reported being male at birth. Regarding sexual orientation, the vast majority, or 93.9%, reported being MSM, with 3.5% reporting being heterosexual men, and 2.6% reporting being heterosexual women. Both HCV positive and HCV negative participants reported a median of 2 sexual partners in the past month; however, the IQR for HCV positive participants was slightly higher (1-4) than HCV negative participants (1-3, p=0.02); additionally, 70.8% of HCV positive participants reported two or more sexual partners in the past month compared to 55.8% of HCV negative participants (p=0.05). At time of HIV diagnosis, median CD4 count at diagnosis was 361 cells/microliter (IQR 264-496), and median HIV RNA level was 5.94 (IQR 5.24-6.75) log 10 copies/ml. Co-infection with other infections at diagnosis was not uncommon: 5.1% were positive for hepatitis B surface antigen and 14.3% had positive TPHA/RPR.
Nine men were HCV antibody positive at time of HIV diagnosis, yielding a baseline HCV prevalence of 1.6% (95% CI 0.7-3.0). Of the prevalent cases, only five had detectable HCV RNA; three (60%) were genotype (GT) 3a and two (40%) were GT1a. No participants who had undetectable HCV RNA reported prior treatment, and likely represent those who spontaneously cleared.

Over the 1883 person-years (PY) of observation in the cohort, 39 HCV incident cases were identified, for an overall incidence of 20.7/1000 PY (95% CI 15.1-28.3/1000 PY). Notably, no incident cases were identified prior to 2014, with incidence increasing from 0/1000 PY in 2009-2013 to a range of 7.5-11.4/1000 PY in the years 2014-2016, 32.3/1000PY in 2017, and then 44.8/1000PY in 2018 (Figure 1, p=0.001). Median time to HCV seroconversion was 1.9 (IQR 0.4-4.2) years. HCV genotype was available for 35 cases, of which 32 (91.4%) were GT1a and 3 (8.6%) were GT3a. Only one incident HCV case (2.1%) was coinfected with hepatitis B.

Recreational drug use in the cohort increased over time. Only 21.3% reported any drug use at time of HIV diagnosis from 2009 to 2018. However, during follow-up visits in 2017-2018, 43.4% reported using one or more drugs in the previous 6 months. Prior to 2017, injection drug use was rarely reported in the cohort; only one participant reported injection drug use (of heroin) at the time of HIV diagnosis, and no injection drug use was reported by any participant during longitudinal follow-up prior to 2017. Since 2017, however, 7 participants reported injecting methamphetamine (no heroin use reported), of whom 2 contracted HCV during follow-up.
In univariate analysis, methamphetamine use, group sex, and any history of positive TPHA/RPR were significantly associated with incident HCV infection (Table 1). Two of the seven participants (28.6%) that reported injecting methamphetamine had incident HCV infection, compared to 6.7% of non-injectors, but the difference was not statistically significant (p=0.083). In multivariate analysis, methamphetamine use [adjusted HR 2.33 (95% CI 1.13 - 4.8), p=0.022], group sex [adjusted HR of 2.54 (95% CI 1.26 - 5.12), p=0.009], and history of positive TPHA/RPR [adjusted HR 2.43 (95% CI 1.22 - 4.85), p=0.012] all remained significantly associated with incident HCV infection.

**Discussion**

Previous studies in Thai MSM have not documented high prevalence or incidence of HCV, and HIV-infected Thai MSM have not previously been considered at high risk for HCV infection (177). The 2017 Thai Guidelines on HIV Diagnosis and Treatment recommend testing for HCV antibody only once at the time of HIV diagnosis; annual testing for HCV antibody is advised only for those who report injecting drug use (178). However, in this analysis we document an alarming epidemic of HCV among a cohort of HIV-infected Thai MSM identified and treated during acute HIV infection. This rapidly emerging HCV epidemic is fueled by methamphetamine use and group sex. Of the incident cases, the vast majority (86.7%, 13/15) who reported methamphetamine use also reported group sex. Additionally, 33.3% (13/39) of all incident case reported group sex and methamphetamine use, compared to 6.7% (35/524) who did not seroconvert HCV antibody (P<0.001). Intravenous injection of methamphetamine was reported by a small proportion of the cohort, and 95% of the Thai MSM who acquired HCV
infection reported no previous injection drug use. Therefore, HCV transmission among MSM in Bangkok appears to be facilitated primarily through sexual contact.

In the era of widespread access to effective ART, changing risk behavior patterns such as increased illicit drug use and more risky sexual behavior have been documented among MSM (179, 180). Combined, these risk factors may amplify transmission of sexually transmitted infections (STIs), including HCV. In previous studies of HCV incidence among HIV-infected MSM who deny injecting drug use, polydrug use, condomless receptive anal intercourse, traumatic or rough sex, recent syphilis infection, and history of other ulcerative STIs have been associated with HCV infection (181, 182). Similar to previous studies, a history of positive TPHA/RPR was associated with incident HCV infection in this cohort. Our study augments the previous literature by emphasizing the role of methamphetamine use specifically in facilitating group sex, with both of these factors being significant for acquisition of HCV after HIV diagnosis.

Chemsex, or the use of drugs such as amphetamine-type stimulants or GHB to enable or enhance sexual intercourse, may decrease inhibition, allowing for an increased number of partners in one session, condomless receptive anal intercourse, and shared use of drug paraphernalia. Crystal methamphetamine, also known as “ice”, has increased in use among young MSM in Bangkok, and has been associated with incident HIV infection, sex work, group sex, and finding casual sex partners on the internet (32). In recent years, a Bangkok-based subculture has developed around “ice parties,” as documented in a recent qualitative study (183). Through a series of in-depth interviews and focus group discussions among over forty young Thai MSM who use ice, this research uncovered multiple risks around ice parties, which
often included having condomless sex with multiple partners for extended periods of time. Coerced sex and exchange of ice for sex was also reported. Concerningly, participants’ fears about ice use focused on avoidance of police and drug overdose; there was little to no concern about the risk of HIV or STI transmission in these settings.

This study has some limitations. Drug use was captured through self-report during a computer-assisted interview during cohort visits or during interview by physicians, and may be underreported by participants. As illicit drug use and needle exchange is criminalized in Thailand with severe penalties for use, injecting may specifically be underreported. Differentiating between recent syphilis infection and treated syphilis in this analysis was difficult due to the timing of TPHA/RPR titres in relation to diagnosis of incident HCV, so any positive TPHA/RPR was used as a marker for past history of syphilis. Finally, as the cohort was comprised entirely of participants identified with acute HIV infection, it selected for those who accessed HIV testing during a period of high risk, most of whom were urban, young MSM with high educational and socioeconomic status. Therefore, the AHI cohort may not be representative of MSM throughout Thailand or within the region.

However, both Bangkok and Pattaya are known as entertainment hubs and tourist destinations for MSM from throughout Thailand and East Asia. Circuit parties, weekend-long social events where MSM gather together, regularly attract over 10,000 MSM to Bangkok or other locations in Thailand at the Western and Thai New Year holidays (184). Increasing HCV incidence among young, sexually-active Thai MSM may presage the beginnings of increased HCV transmission in the region and beyond (185).
Given the increasing HCV incidence noted in this cohort, standardized annual antibody screening for HCV infection among HIV-infected MSM would be of great value in detecting early infection. Clinicians providing care to HIV-infected MSM in Thailand should include questions about high risk sexual behavior, such as group sex or methamphetamine use, in patient interviews in order to guide risk reduction counseling and increase identification of incident HCV cases. Those identified with HCV should be referred for treatment.

In conclusion, this study documents an alarming rise in the incidence of HCV in a cohort of Thai MSM living with HIV. Incident HCV infection was associated with methamphetamine use, group sex, and a history of syphilis. To decrease HCV-related morbidity among HIV-infected MSM, urgent efforts are needed to provide education and harm reduction to at-risk MSM who are engaging in drug use and/or group sex, increase identification of incident HCV cases, and ensure access to pan-genotypic DAA treatment.

Note: This paper was published ahead of print as a first-author manuscript in JAIDS in April 2020.
### Table 4-1: Baseline Characteristics of all Anti-HCV Negative and Anti-HCV Positive Participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (N=573)</th>
<th>Anti-HCV - (N=525)</th>
<th>Anti-HCV + (N=48)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>26 (22 – 31)</td>
<td>26 (22 – 31)</td>
<td>25 (22 – 31)</td>
<td>0.599</td>
</tr>
<tr>
<td>Sex Assigned at birth, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.658</td>
</tr>
<tr>
<td>Female</td>
<td>15 (2.6)</td>
<td>15 (2.9)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>558 (97.4)</td>
<td>510 (97.1)</td>
<td>48 (100.0)</td>
<td></td>
</tr>
<tr>
<td>Behavior risk, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.776</td>
</tr>
<tr>
<td>MSM</td>
<td>538 (93.9)</td>
<td>491 (93.5)</td>
<td>47 (97.9)</td>
<td></td>
</tr>
<tr>
<td>Heterosexual male</td>
<td>20 (3.5)</td>
<td>19 (3.6)</td>
<td>1 (2.1)</td>
<td></td>
</tr>
<tr>
<td>Heterosexual female</td>
<td>15 (2.6)</td>
<td>15 (2.9)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Number of sexual partners in the past month, median (IQR)</td>
<td>2 (1 – 3)</td>
<td>2 (1 – 3)</td>
<td>2 (1 – 4)</td>
<td>0.017</td>
</tr>
<tr>
<td>More than 1 sexual partner in the past month</td>
<td>327 (57.1)</td>
<td>293 (55.8)</td>
<td>34 (70.8)</td>
<td>0.048</td>
</tr>
<tr>
<td>Group sex, n (%)</td>
<td>111 (19.4)</td>
<td>90 (17.1)</td>
<td>21 (43.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Drug use, n (%)</td>
<td>122 (21.3)</td>
<td>101 (19.2)</td>
<td>21 (43.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hepatitis B surface antigen positive</td>
<td>29 (5.1)</td>
<td>28 (5.3)</td>
<td>1 (2.1)</td>
<td>0.499</td>
</tr>
<tr>
<td>History of syphilis</td>
<td>82 (14.3)</td>
<td>73 (13.9)</td>
<td>9 (18.8)</td>
<td>0.387</td>
</tr>
<tr>
<td>Fiebig stage, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.87</td>
</tr>
<tr>
<td>I</td>
<td>81 (14.1)</td>
<td>75 (14.3)</td>
<td>6 (12.5)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>130 (22.7)</td>
<td>122 (23.2)</td>
<td>8 (16.7)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>259 (45.2)</td>
<td>234 (44.6)</td>
<td>25 (52.1)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>67 (11.7)</td>
<td>61 (11.6)</td>
<td>6 (12.5)</td>
<td></td>
</tr>
<tr>
<td>V-VI</td>
<td>36 (6.3)</td>
<td>33 (6.3)</td>
<td>3 (6.3)</td>
<td></td>
</tr>
<tr>
<td>CD4 T cells* (cells/µL), median (IQR)</td>
<td>361 (264 – 496)</td>
<td>361 (265 – 505)</td>
<td>360 (234 – 470)</td>
<td></td>
</tr>
<tr>
<td>HIV RNA at time of HIV diagnosis (log10copies/mL), median (IQR)</td>
<td>5.94 (5.24 – 6.75)</td>
<td>5.93 (5.23 – 6.73)</td>
<td>6.06 (5.39 – 6.89)</td>
<td></td>
</tr>
</tbody>
</table>

Anti-HCV+ includes both prevalent (n=9) and incident (n=39) cases. Abbreviations: Anti-HCV, Hepatitis C antibody, MSM, men who has sex with men, Group sex defined as having at least two other partners during one sexual encounter, Drug use defined as any illicit or nonprescription drug use in month prior to diagnosis, Syphilis defined as positive TPHA/RPR at time of HIV diagnosis.
<table>
<thead>
<tr>
<th>Factors</th>
<th>Total (N=563)</th>
<th>No (N=524)</th>
<th>Incident HCV (N=39)</th>
<th>Univariate HR (95%CI)</th>
<th>p-value</th>
<th>Multivariate Adjusted HR (95%CI)</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Age, years (IQR)</td>
<td>26 (22-31)</td>
<td>26 (23-31)</td>
<td>25 (22-31)</td>
<td>0.98 (0.93 – 1.02)</td>
<td>0.346</td>
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<td>Fiebig stage</td>
<td></td>
<td></td>
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<tr>
<td>I</td>
<td>78 (13.9)</td>
<td>74 (14.1)</td>
<td>4 (10.3)</td>
<td>Ref.</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>II</td>
<td>130 (23.1)</td>
<td>122 (23.3)</td>
<td>8 (20.5)</td>
<td>1.01 (0.30 – 3.37)</td>
<td>0.985</td>
<td></td>
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<tr>
<td>III</td>
<td>254 (45.1)</td>
<td>234 (44.7)</td>
<td>20 (51.3)</td>
<td>1.64 (0.56 – 4.80)</td>
<td>0.369</td>
<td></td>
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<tr>
<td>IV</td>
<td>65 (11.6)</td>
<td>61 (11.6)</td>
<td>4 (10.3)</td>
<td>1.39 (0.35 – 5.59)</td>
<td>0.640</td>
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<tr>
<td>V-IV</td>
<td>36 (6.4)</td>
<td>33 (6.3)</td>
<td>3 (7.7)</td>
<td>1.69 (0.38 – 7.58)</td>
<td>0.490</td>
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<tr>
<td>Group sex†</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>456 (81.0)</td>
<td>434 (82.8)</td>
<td>22 (56.4)</td>
<td>Ref.</td>
<td></td>
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<td></td>
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<tr>
<td>Yes</td>
<td>107 (19.0)</td>
<td>90 (17.2)</td>
<td>17 (43.6)</td>
<td><strong>3.74 (1.99 – 7.08)</strong></td>
<td>&lt;0.001</td>
<td><strong>2.54 (1.26 – 5.12)</strong></td>
<td>0.009</td>
</tr>
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<td>Risky alcohol use†</td>
<td></td>
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<tr>
<td>No</td>
<td>367 (65.2)</td>
<td>341 (65.1)</td>
<td>26 (66.7)</td>
<td>Ref.</td>
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<tr>
<td>Yes</td>
<td>196 (34.8)</td>
<td>183 (34.9)</td>
<td>13 (33.3)</td>
<td>0.87 (0.44 – 1.69)</td>
<td>0.677</td>
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<td>Methamphetamine use†</td>
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<tr>
<td>No</td>
<td>465 (82.6)</td>
<td>441 (84.2)</td>
<td>24 (61.5)</td>
<td>Ref.</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Yes</td>
<td>98 (17.4)</td>
<td>83 (15.8)</td>
<td>15 (38.5)</td>
<td><strong>4.05 (2.10 – 7.79)</strong></td>
<td>&lt;0.001</td>
<td><strong>2.33 (1.13 – 4.80)</strong></td>
<td>0.022</td>
</tr>
<tr>
<td>Drug injection†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>556 (98.8)</td>
<td>519 (99.1)</td>
<td>37 (94.9)</td>
<td>Ref.</td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>7 (1.2)</td>
<td>5 (0.9)</td>
<td>2 (5.1)</td>
<td>3.65(0.84 – 15.78)</td>
<td>0.083</td>
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<tr>
<td>TPHA/RPR†</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>343 (60.9)</td>
<td>331 (63.2)</td>
<td>12 (30.8)</td>
<td>Ref.</td>
<td></td>
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<td>Yes</td>
<td>220 (39.1)</td>
<td>193 (36.8)</td>
<td>27 (69.2)</td>
<td><strong>3.02 (1.53 – 5.96)</strong></td>
<td>0.001</td>
<td><strong>2.43 (1.22 – 4.85)</strong></td>
<td>0.012</td>
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*Total N includes excludes prevalent hepatitis C cases and one case that withdrew from cohort immediately after enrollment. Legend: HR, hazard ratio; significant HR are presented in bold. For all factors designated by †, the factor was counted as ‘yes’ if participant reported these behaviors or, in the case of TPHA/RPR, tested positive at one or more time points during follow up. Group sex was defined as having at least two other partners during one sexual encounter, methamphetamine use included both non injecting and injecting drug use, risky alcohol use was defined by AUDIT-C.
Chapter 5: Conclusion
Antiretroviral therapy has dramatically altered the prognosis for those living with HIV/AIDS. In the United States, a 20-year old with HIV diagnosed in the early 2000s was expected to live between 36-39 years of age; in the past decade, that has increased to close to 70 years (186). Despite these gains, the syndemic of viral hepatitis and substance use among people living with HIV continues to have an enduring effect on both morbidity and mortality. In the North American NA-ACCORD cohort, those with a history of injecting drug use had a disparity of survival of approximately one decade compared to those with no history of use(187). Modeling revealed the prevention of 20% of drug-and-alcohol deaths could narrow, but not eliminate, the differences in mortality. Other comorbidities, including viral hepatitis, could contribute to persistent gaps in mortality in co-infected individuals. The work presented in this dissertation provides insights into how substance use can impact acquisition and treatment of viral hepatitis co-infection in individuals living with HIV.

In Chapter 2, we examined barriers to receipt of HCV treatment among HIV/HCV coinfected patients in the Johns Hopkins Clinical Cohort during the interferon era. Our case-control analysis revealed many factors that would not be changed by the removal of interferon alone. Non-whites, those who reported recent active drug use, and those with low level of engagement in clinical care (measured by percentage of missed visits) were significantly less likely to have initiated HCV treatment. In the DAA era, HCV treatment uptake has increased, and of 593 HIV/HCV patients engaged in HIV care between 2013-2016, 72% initiated treatment, and 62% achieved SVR(188). Despite increased uptake, engagement in clinical care remained the most predictive factor of whether or not a coinfected patient would initiate treatment for HCV; those who missed more scheduled visits were least likely to be treated for HCV.
Prior studies have shown that HIV accelerates the development of cirrhosis and hepatocellular carcinoma, increasing morbidity and mortality in co-infected individuals. Globally, by 2040, HBV and HCV are projected to cause more deaths than HIV, tuberculosis, and malaria combined(189). Advances in HBV and HCV treatment have galvanized global health organizations to set goals for hepatitis elimination, with the aim to reduce incidence by 90% and hepatitis-related deaths by 65% between 2015 and 2030(190).

In Chapter 3, we examined the impact of HBV and/or HCV co-infection on survival in the early and later antiretroviral treatment eras, which was marked by the introduction of HBV-active ART (tenofovir) as well as pegylated-interferon treatment for HCV. In this study, HIV/HBV, HIV/HCV, and HIV/HBV/HCV triply infected patients continued to suffer from increased mortality compared to HIV mono-infected individuals. Notably, not all excess mortality could be attributed to liver-related mortality, and other causes, such as septicemia and drug-related deaths, contributed to disparities in mortality in coinfected patients. Further research needs to be conducted to evaluate whether time on tenofovir (for HBV coinfected patients) or HCV cure in the post-DAA era (for HCV coinfected patients) impacts mortality. For this cohort, we are currently evaluating mortality among HCV coinfected patients in the post-DAA era, and plan to combine updated mortality data with the findings in Chapter 3 for publication.

In Chapter 4, we documented an emerging epidemic of hepatitis C in a cohort of Thai MSM who entered care during acute HIV infection. Noninjecting use of methamphetamine, group sex, and syphilis were strongly associated with incident HCV infection. Our findings
support increased screening for both ATS use and HCV in this population and highlight the need for harm reduction interventions addressing the developing chemsex culture in the MSM community. Further studies are currently being done to elucidate HCV transmission networks in Bangkok-based HIV cohorts.

In conclusion, major advances have been made in the treatment of HIV, HBV, and HCV in the past two decades. However, people who use drugs continue to bear a disproportionate burden of HIV and viral hepatitis co-infection. The research presented in this dissertation provides insight into disparities contributing to morbidity and mortality among HBV and/or HCV coinfected people living with HIV, and highlights potential areas for future research to mitigate harms related to substance use and viral hepatitis.

In order to attain targets for the elimination of chronic hepatitis B and C, a comprehensive approach must be taken to provide harm reduction services for people who use drugs, including needle and syringe exchange and access to medication-assisted treatment. HBV vaccination should be prioritized in high-risk groups such as MSM and PWID who were born prior to the rollout of birth dose HBV vaccination. In addition, ongoing surveillance for incident infection is needed. Although HCV is now a curable disease, reinfection is possible and not uncommon in groups who engage in high risk behaviors such as injecting drug use and group sex(191, 192). Expansion of testing and treatment for HBV and HCV, and continued efforts to increase and sustain engagement in clinical care for those coinfected with HIV, is necessary to achieve meaningful reductions in morbidity and mortality attributed to chronic hepatitis globally.
References


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58. WHO. Dolutegravir (DRG0 and the fixed dose combination (FDC) of tenofovir/lamivudine/dolutegravir (TLD). 2018.


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Curriculum Vitae

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Education/Training:

<table>
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<tr>
<th>Institution and Location</th>
<th>Degree</th>
<th>Year completed</th>
<th>Field of Study</th>
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<tr>
<td>Johns Hopkins Bloomberg School of Public Health, Baltimore, MD</td>
<td>Ph.D.</td>
<td>2020</td>
<td>Clinical Investigation</td>
</tr>
<tr>
<td>Johns Hopkins Hospital, Baltimore, MD</td>
<td>Fellowship</td>
<td>2014</td>
<td>Infectious Diseases</td>
</tr>
<tr>
<td>Johns Hopkins Bayview Medical Center, Baltimore, MD</td>
<td>Residency</td>
<td>2012</td>
<td>Internal Medicine</td>
</tr>
<tr>
<td>University of Michigan Medical School, Ann Arbor, MI</td>
<td>M.D.</td>
<td>2009</td>
<td>Medicine</td>
</tr>
<tr>
<td>Gerald R. Ford School of Public Policy at the University of Michigan, Ann Arbor, MI</td>
<td>M.P.P.</td>
<td>2009</td>
<td>Health Policy</td>
</tr>
<tr>
<td>Swarthmore College, Swarthmore, PA</td>
<td>B.A.</td>
<td>2002</td>
<td>Chinese Studies, Biology</td>
</tr>
</tbody>
</table>
**Professional Experience:**

**Director, Research and Advocacy, Dreamlopmements, Bangkok, Thailand**

*February 2019-present*

**Responsibilities:**

- Protocol chair of C-Free Protocol, study enrolling up to 3000 people who use drugs and their partners for point-of-care HIV and viral hepatitis testing and treatment with antiretrovirals (HIV) and direct-acting antivirals (generic sofosbuvir/velpatasvir) for HCV at community-based drop-in centers run by key populations (former and current people who use drugs through Raks Thai Foundation and Ozone Foundation).
- Provide technical guidance on research operations and implementation, serve as study physician at community drop-in center, and engage community members through education, training, and capacity building for key population led health services.
- Volunteer Clinical Trial Physician at HIV Netherlands-Australia-Thailand (HIV NAT) for AIDS Clinical Trial Group (ACTG) trials enrolling at the Thai Red Cross, focus on viral hepatitis and HIV co-infection.

**Consultant, Expert on Sexually Transmitted Infections and Pre-Exposure Prophylaxis (STI/PrEP), PATH/USAID, Hanoi, Vietnam**

*March 2019-present*

- Created SOPs and training curriculum regarding diagnosis and treatment of common STIs
- Provided technical assistance regarding pooled diagnostics for gonorrhea and chlamydia
- Lead trainer for comprehensive two-day training for physicians, nurses, and community workers at both governmental and non-governmental clinics
- Guest on Galant Clinic facebook livestream to discuss PrEP and STIs, video with 2400+ views on facebook.
- Serve as online mentor and educator for clinic staff
- Assist with writing medical manuscripts on PrEP and STIs in Vietnam

**Senior Medical Officer, Siriraj Institute for Clinical Research (SicRES)**

*April 2020-present*

- Medical monitor for four Thai sites participating in multinational zoliflodacin trial for treatment of gonorrhea infection
- Trial sponsored by Drugs for Neglected Diseases Initiative (DnDI) and Global Antibiotic Research and Development Partnership (GARDP)
- Deliver protocol, safety monitoring, and safety reporting training at site initiation visits, and provide on-site training and monitoring to clinical sites without prior research experience
- Review eCRF for eligibility, safety and efficacy data, protocol deviations
- Provide DSMB support as needed
United Nations Locums Medical Officer, United Nations Economic and Social Commission for Asia and the Pacific (UNESCAP), Bangkok, Thailand
January 2018-present
Responsibilities:
- Provide walk-in consultations and vaccination advice to UN Staff
- Ensure medical documentation and standards complete to process both employment and travel related clearance for multiple UN agencies
- Supervise clinic nurse

Director, Clinical Research Division, Department of Retrovirology, and Research Physician, Department of Retrovirology, Henry M. Jackson Foundation in support of the US Military HIV Research Program, Bangkok, Thailand
August 2015-January 2019
Responsibilities:
- Supervise departmental clinical operations group, providing operational support to collaborating field sites and handles all regulatory submissions and continuing reviews to the Human Subjects Protection Board and Walter Reed Army Institute of Research IRB, represent department to key collaborators, including Thai Red Cross AIDS Research Centre, Royal Thai Army, Vaccine Trial Centre at Mahidol University, and Dept of HIV Vaccines at Thai Ministry of Public Health. Provide leadership and central coordination to ECHO (Early Capture HIV Cohort) staff in Pattaya. Lead community stakeholder engagement team, including providing high level input to annual stakeholder engagement plans, providing education and information into good participatory practice (GPP) implementation to community stakeholders such as SISTERS transgender NGO, and assisting with programming for Retrovirology Community Advisory Board.
- Protocol chair of RV348, a cohort study enrolling 2000 high-risk men who have sex with men (MSM) and transgender women (TGW) at four sites in Thailand to assess feasibility for future HIV vaccine efficacy studies. Primary objectives of cohort are to measure HIV incidence in this population and retention over 18 months. Responsible for regulatory submissions, budget, operational site support, and implementation as sponsor representative.
- Examine volunteers as study physician at SEARCH/Thai Red Cross AIDS Research Centre, consult on HIV and therapeutic management.
- Serve as department representative on Armed Forces Research Institute of Medical Sciences Institutional Biosafety Committee

Academic Appointments:
Instructor in Medicine, Division of Infectious Diseases, Johns Hopkins School of Medicine 2014-2015
Academic and Research Awards:
Award amount covers full tuition at JHSPH, stipend, and research support
Research and Clinical Focus: HIV and viral hepatitis co-infection
Mentor: Mark Sulkowski, MD
Total award amount: $200,000

Bristol Myers Squibb Virology Fellows Grant 2013-2014
Project: HCV Treatment in an Urban HIV Clinic: Patient and Health Care Provider Determinants of Receipt of Therapy, 2002 to 2013
Award amount: $20,000

American College of Physicians Maryland Associates Annual Meeting 2011
First Place, Oral Clinical Vignette Competition
“Hemophagocytic lymphohistiocytosis secondary to disseminated tuberculosis infection”
Award amount: $1000

University of Michigan Rackham Graduate School Merit Fellowship 2008-2009
Full tuition for Master in Public Policy at Gerald R. Ford School of Public Policy
Award amount: $20,000

CDC OC Hubert Fellowship in International Health 2008
Host Institution: CDC/Thai Ministry of Public Health Emerging Infectious Diseases Collaboration, Nonthaburi, Thailand
Award Amount: $5000

NIH/Fogarty International Center Clinical Research Fellowship 2006-2007
Host Institutions: Research Institute for the Health Sciences, Chiang Mai University, Chiang Mai, Thailand and Johns Hopkins Bloomberg School of Public Health
Award amount: $35,000

Duke University Global Health Policy Fellowship 2006
Host Institution: World Health Organization Department on Essential Drugs
Mentor: Cecilia Oh, LLM
Award amount: $8,000

Fulbright Scholarship 2002-2003
Project: Advocacy, Activism, and Clinical Research: Ethics of HIV Testing and Care among Marginalized Populations in Bangkok, Thailand
Award amount: $40,000

Alice Crossley Prize for best paper submitted in Asian Studies, Swarthmore College
Thesis: Taking a Holistic View of the Chinese-American Health Care Experience: Contextualizing the individual cultural construction of health and illness within immigrant communities

Conference and Travel Awards:
CROI International Investigator Scholarship 2020
IAS International Investigator Scholarship 2019
CROI Young Investigator Scholarship 2014
NIAID/IDSA Research Careers Meeting for Selected ID Fellows 2013
NIDA/Boston University Scholarship: Fellow Immersion Training Program on Addiction Medicine, HIV, and Hepatitis C 2011
Johns Hopkins Center for Global Health Travel Award 2011
University of Michigan Global Health Research and Training Graduate Award 2006
International Health Medical Education Consortium Poster Award 2004
New York Academy of Medicine David E. Rogers Fellowship 2004
IAS Conference Student Scholarship 2002

Leadership Awards:
JW Saxe Memorial Prize for Public Service 2009
Michigan Campus Compact Heart and Soul Award 2008
University of Michigan Outstanding Student Leader Award 2006
University of Michigan Tapestry Award for Commitment to Diversity 2005
Swarthmore Intercultural Center Lifetime Leadership Award 2002
Dean’s Award for Leadership and Community Service, Swarthmore College 2002

**Board Certifications:**
Diplomat, American Subspecialty Board of Infectious Disease 2015

Diplomat, American Board of Internal Medicine 2012

**Medical Licensure:**
State of Maryland License #D78462 2014-current

**Professional Memberships:**
International AIDS Society (IAS) 2019

Infectious Diseases Society of America (IDSA) 2012

American Association for the Study of Liver Disease (AASLD) 2013

American College of Physicians (ACP) 2009

**Publications:**


**Oral Presentations and Invited Talks:**


Thailand, TRIPS (Trade Related Aspects of Intellectual Property Rights), and Compulsory Licensing. Oral Presentation presented at: United States Social Forum: International People's Health Mini-Course; Atlanta, GA, 2007

Plenary Session: Student Opportunities for Working Abroad. Global Health Education Consortium Annual Meeting; San Francisco, CA, 2005
Poster Presentations:


Leadership Experience:

Investigator representing Thai Red Cross AIDS Research Centre (TRCARC) for US NIH-sponsored AIDS Clinical Trials Group (ACTG), elected member of Hepatitis Transformative Science Group 2018-current

AVAC (AIDS Vaccine Advocacy Coalition) Good Participatory Practices Implementer’s Course 2017-2018

Chair of External Advisory Board for COPE4YMSM study, cost-effectiveness study of PrEP in male and transgender sex workers run by Johns Hopkins University in conjunction with Thai-US Centers for Disease Control & selected community-based organizations 2016-current
Invited member of Scientific Advisory Committee for PULSE, 3 year research advocacy and capacity building initiative led by APCOM to collect epidemiological and behavioural data on young MSM in the Greater Mekong subregion

Invited medical consultant to MSM Community Advisory Board (M-CAB) 2017-2018

Invited steering committee member for FHI360 PrEP Crowdsourcing Contest Project 2018

**Community Health Education Experience:**

Transgender Health Community Education Workshops at SISTERS, Pattaya
Provided information on antiretroviral therapy and hormone interactions, genital affirmation surgery 2017-2018

Johns Hopkins Bayview Program for Lay Health Educators Trainer 2011-2012

Baltimore City Department of Public Health HIV Retention and Outreach Volunteer 2009

Planned Parenthood Association of Thailand Medical Volunteer 2006-2007

Michigan Governor’s Council on Asian Pacific American Affairs
Immigrant Health Policy Brief Intern 2006

Students Teaching AIDS to Students Medical School Coordinator 2003-2005

EMPOWER Thailand: English Teacher and Sexual Health Educator for Commercial Sex Workers 2002-2003

**Language Proficiency:**

English: Native fluency (speaking, reading, writing)

Thai: fluent speaking, basic reading, minimal writing

Mandarin Chinese: basic speaking, minimal reading and writing