686

Association of Co-infection with HBV, HCV, or Both on Survival among HIV-Infected Adults

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REVISED ABSTRACT

Background: HBV and HCV co-infection is associated with increased morbidity and, in some studies, with increased mortality in HIV-infected patients. The impact of highly active antiretroviral therapy (HAART) on this relationship is incompletely defined. We examined survival among adults who were infected with HIV alone or in conjunction with HBV, HCV, or both.

Methodology: Prospective cohort study of 4819 patients with HIV and known HBV and HCV status receiving care at the Johns Hopkins HIV Clinic from January 1996 to March 2013. Chronic HBV infection was defined as any HbsAg positive result. HCV infection was defined as HCV antibody positive or detectable HCV RNA. The primary outcome was all-cause mortality rates per 1000 person years according to infection status: HIV alone, HBV/HIV, HCV/HIV and HCV/HBV/HIV. We performed analyses with Poisson regression comparing early (1996-2002) vs. modern (2002-2013) HAART and a combined analysis for the entire time period.

Results: For the entire time period (1996-2013), at time of clinic enrollment, patients with HCV (n=1961, 40.7%) were older (median age, 42 years vs. 38 years) than those with HIV alone (n=2458, 51.0%) . As shown in figure 3, unadjusted crude mortality rates were higher in patients with HBV/HIV (n=82, 63.2 deaths per 1000 PYs, 95% CI 50.9-78.5), HCV/HIV (n=733, 56.1 deaths per 1000 PYs, 95% CI 52.1-60.3) and HCV/HBV/HIV (n=74, 69.3 deaths per 1000s PYs, 95% CI 55.2-87.1) compared to those with HIV alone (35.3 deaths per 1000 PYs; 95% CI 32.4-38.4). After adjustment for potential confounders, mortality rate was independently associated with HCV coinfection (adjusted incidence rate ratio [IRR] 1.23, 95% CI 1.09-1.38), HBV coinfection (IRR 1.57, 95% CI 1.24-1.99),HCV/HBV/HIV coinfection (IRR 1.45, 95% CI 1.13-1.85) , age (IRR 1.44, 95% CI 1.23-1.68), injecting drug use (IRR 1.93, 95% CI 1.6-2.7), and HAART status (IRR 2.31 for VL undetectable for 0-25% of all visits; 95% CI 1.9-2.8).

Conclusions: In the modern HAART era, HIV positive patients coinfected with HBV, HCV, or both had higher incidence of death compared to those with HIV alone after adjustment for HIV disease status, treatment status, and other potential confounders.

BACKGROUND & OBJECTIVE

Background

- While modern HAART has contributed to major declines in HIV-related morbidity and mortality, its effect on HIV-positive patients co-infected with HBV, HCV, or both is not well characterized.
- HIV co-infection accelerates the progression of liver disease and cirrhosis in patients with HBV and HCV.

Objective

- Compare mortality rates and causes of mortality between HIV mono-infected, HIV/HBV co-infected, HIV/HCV co-infected, and HIV/HBV/HCV tri-infected patients in the early and modern HAART eras.

METHODS

Study Population

- All patients enrolled at the Johns Hopkins HIV Clinic between January 1996 and March 2013 (n=4819)

Definitions of Infection Status

- Hepatitis B defined as any positive Hepatitis B Surface Antigen
- Hepatitis C defined as Hepatitis C Antibody positive or HCV RNA detectable
- Patients without known HBV or HCV status were excluded

Mortality

- We analyzed patient data according to two discrete time periods: 1996-2002 (early HAART) and 2002- 2013 (modern HAART). A combined analysis was also performed.
- Mortality data were ascertained through the National Death Index Plus (89.2%), medical record review (8.9%), death certificate (0.8%), and autopsy (1.1%). The primary cause of death was available for the majority of the 1420 deaths observed (79.6%).
- Incidence rates of all-cause mortality per 1000 person-years were calculated according to infection status
- Poisson regression was used to calculate incidence rate ratios in model controlling for age, race, CD4 count, and HAART use.

TABLE 3: Adjusted Incidence Rate Ratios of Mortality by HAART Era and Covariate Status*

Covariate	Combined IRR (95% CI)	Early HAART IRR (95% CI)	Modern HAART IRR (95% CI)
Female gender	0.98 (0.87-1.09)	1.00 (0.80-1.3)	0.97 (0.85-1.10)
African-American	1.10 (0.95-1.26)	1.11 (0.95-1.26)	1.10 (0.93-1.29)
Infection status			
HIV alone	REF	REF	REF
HIV/HBV	1.57 (1.25-1.99)	1.27 (0.81-2.00)	1.74 (1.33-2.29)
HIV/HCV	1.23 (1.10-1.38)	1.07(0.86-1.35)	1.31 (1.14-1.49)
HIV/HBV/HCV	1.45 (1.13-1.85)	1.58 (1.13-1.85)	1.39 (1.03-1.88)
Age (years)			
<40	REF	REF	REF
40-44	1.33 (1.16-1.52)	1.25 (0.95-1.66)	1.34 (1.16-1.57)
45-49	1.44 (1.23-1.68)	1.60 (1.16-2.21)	1.38 (1.15-1.65)
>50	1.91 (1.64-2.22)	2.62 (1.94-3.56)	1.71 (1.43-2.05)
CD4 count (cells/mm^3)			
<200	REF	REF	REF
200-349	0.33 (0.28-0.38)	0.18 (0.13-0.26)	0.38 (0.33-0.45)
350+	0.18 (0.16-0.21)	0.15(0.11-0.20)	0.19(0.17-0.23)
HIV-RNA <400 (% of total visits)			
>75	REF	REF	REF
26-75	1.37 (1.13-1.66)	1.01 (0.58-1.76)	1.43 (1.16-1.75)
0-25	2.31 (1.93-2.77)	2.22 (1.36-3.62)	2.35 (1.92-2.87)

*Poisson regression model calculating IRR of mortality by HAART era, controlling for gender, race, age, time-varying CD4, and HAART use.

RESULTS

TABLE 1. Characteristics at time of HIV clinic enrollment, 1996-2002

Characteristic	HIV (n=1118)	HIV/HBV (n=120)	HIV/HCV (n=1100)	HIV/HBV/HCV (n=111)
Median age (interquartile range)	36 (31 – 42)	35 (32 – 40)	39 (35 – 44)	39 (34– 44)
Female gender (%)	367 (32.8)	19 (5.8)	375 (34.1)	24 (21.6)
African-American	774 (69.2)	85 (70.8)	920(83.6)	88 (79.3)
Self-reported risk category				
IVDU	80 (7.2)	14 (11.7)	875 (79.6)	87 (78.4)
MSM	446 (39.9)	67 (55.8)	128 (11.6)	22 (19.8)
Heterosexual	565 (50.5)	43 (35.8)	541 (49.2)	46 (41.4)
Median CD4 count (IQR)	237 (65-454)	137 (43-357)	276 (104-459)	272 (55-445)
<200	502(45.1)	69 (57.5)	424 (38.8)	46 (41.8)
200-349	211(19.0)	20 (16.7)	255 (23.3)	24 (21.8)
350+	400 (35.9)	31 (25.9)	414 (37.9)	40 (36.4)
On HAART	396 (35.4)	50 (41.7)	276 (25.1)	30 (27)
HIV RNA<400	173 (16.1)	21 (18.1)	153 (14.7)	15(14.2)

TABLE 2. Characteristics at time of HIV clinic enrollment, 2002-2013*

Characteristic	HIV (n=2213)	HIV/HBV (n=200)	HIV/HCV (n=1718)	HIV/HBV/HCV (n=135)
Median age (interquartile range)	39 (32 – 46)	39 (35 – 46)	44 (39 – 49)	43 (38– 47)
Female gender (%)	793 (35.8)	44 (22.0)	598 (34.8)	27 (20.0)
African-American	1577 (71.3)	149 (74.5)	1396 (81.3)	105 (77.8)
Self-reported risk category				
IVDU	119 (5.4)	23 (11.5)	1285 (74.8)	99 (73.3)
MSM	819 (37.0)	87 (43.5)	203 (11.8)	29 (21.5)
Heterosexual	1207 (54.5)	98 (49.0)	861 (50.1)	51 (37.8)
Median CD4 count (IQR)	321 (152-502)	261 (76-464)	301 (136-504)	276 (103-420)
<200	692 (31.3)	86 (43.0)	579 (33.7)	55 (40.7)
200-349	496 (22.4)	39 (19.5)	409 (23.8)	32 (23.7)
350+	1025 (46.3)	75 (37.5)	730 (42.5)	48 (35.6)
On HAART	1141 (51.6)	113 (56.5)	888 (51.7)	70 (51.9)
HIV RNA<400	728 (32.9)	66 (33.0)	565 (32.9)	31 (77.0)

*Sample size for each group includes patients who enrolled in clinic between 2002-2013 and patients who enrolled prior to 2002. For patients who enrolled prior to 2002, their characteristics for the first visit during 2002-2013 were included in these summary statistics.

FIGURE 1 Probability of Survival after Clinic Enrollment by Infection Status (1996-2002)

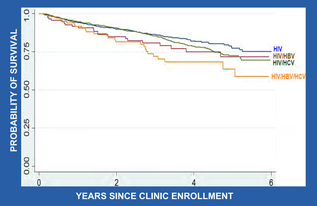


FIGURE 2 – Primary Cause of Death, 1996-2002 (n=194)

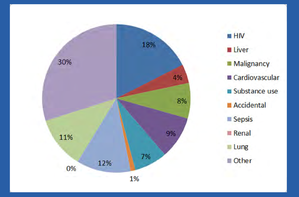


FIGURE 3 – Incidence Rates of All-Cause Mortality by Infection Status and Date of Clinic Enrollment

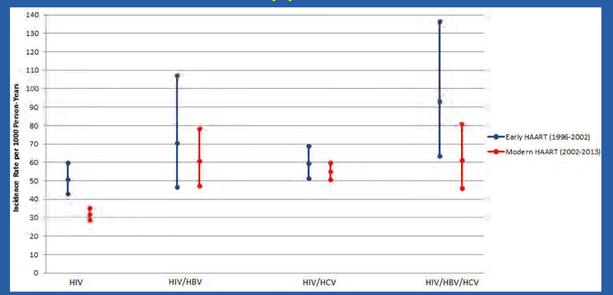


FIGURE 4 Probability of Survival after Clinic Enrollment by Infection Status (2002-2013)

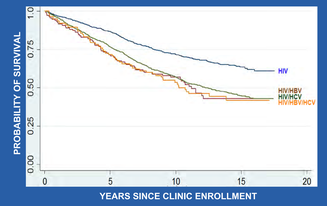
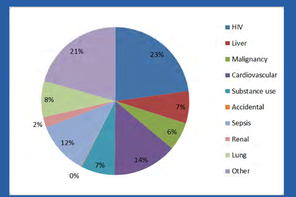


FIGURE 5 – Primary Cause of Death, 2002-2013 (n=937)



CONCLUSION

- HAART substantially reduced mortality in HIV mono-infected patients in the modern era (Incidence rate per 1000 person years, 50.6 in early vs. 31.9 in modern).
- HIV/HBV co-infected patients presented to care much later than HIV mono-infected patients and HIV/HCV co-infected patients in both the early and modern HAART eras.
- After controlling for HIV disease (CD4 cell count) and treatment (HAART use), mortality was similar among HIV-infected patients with and without viral hepatitis in the early HAART era. However, in the modern HAART era, after adjusting for HIV disease and treatment, mortality was significantly increased among HIV/HBV, HIV/HCV, and HIV/HBV/HCV co-infected patients when compared to HIV mono-infected patients.

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