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Survival of HIV-positive individuals with hepatitis B and C infection in Michigan

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SUMMARY

We sought to estimate mortality and associated factors in HIV-hepatitis co-infected individuals in Michigan using a retrospective cohort study. For the study period of 1 January 2006 to 31 December 2009, all HIV-infected individuals were matched to hepatitis B and C cases. In the final Cox proportional hazards regression model, individuals of other [hazard ratio (HR) 2·2, 95% confidence interval (CI) 1·4–3·2] and black (HR 1·3, 95% CI 1·1–1·6) race had decreased survival compared to white race. Similarly, injecting drug users (IDUs) (HR 2·1, 95% CI 1·6–2·6), men who have sex with men (MSM)/IDUs (HR 1·5, 95% CI 1·1–2·2), individuals with undetermined risk (HR 1·5, 95% CI 1·2–1·9) and heterosexual practices (HR 1·4, 95% CI 1·1–1·8) had decreased survival compared to MSM. Additionally, an interaction was found between current HIV status and co-infection. Mortality in HIV-hepatitis co-infected individuals remains a continuing problem. Our study can help in planning interventions to reduce mortality in HIV-infected individuals.

Key words: Hepatitis, HIV/AIDS, infectious disease, surveillance.

INTRODUCTION

By the end of 2009, 33·3 million people were living with HIV infection globally. There were 1·8 million deaths due to HIV/AIDS in 2009 [1]. In the same year, an estimated 1·2 million people were living with AIDS in the USA while about 17 000 AIDS-related deaths were reported [2]. According to the Michigan Department of Community Health (MDCH), there are an estimated 19 500 people currently living with HIV/AIDS in Michigan [3].

Hepatitis B virus (HBV) and hepatitis C virus (HCV) co-infections are relatively common in individuals diagnosed with HIV/AIDS because of shared transmission routes [4–6]. More importantly, these co-infections have emerged as major contributors to morbidity and mortality in HIV/AIDS patients [7]. However, the association between hepatitis co-infection and increased mortality has not been consistently assessed. Studies conducted in USA [8] and South Africa [9] did not show an association between

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such co-infection and mortality. Nonetheless, some studies which did not identify an association between HIV/HCV infection and mortality did report an association between AIDS and mortality [10, 11].

There is increasing evidence to support the association between co-infection and increased liver-related mortality. Studies conducted on HIV and HBV or HCV co-infections have identified a significant association between these co-infections and liver-related mortality [12–17] and some have also reported an increased risk for all-cause mortality and co-infection [15, 17].

Other studies focusing upon HBV and HCV co-infection have reported an association between co-infection and non-liver-related mortality. A decreased survival was reported in AIDS patients co-infected with HBV or HCV [18]. The Swiss HIV Cohort Study reported an increased progression to new AIDS defining event and death in HIV-1-infected patients with HCV co-infection [19]. HIV/HCV co-infection in injecting drug users (IDUs) was also identified as a significant contributor to mortality in the highly active anti-retroviral therapy (HAART) era [20]. HIV and HBV co-infected patients were also found to have an increased risk of death after initiation of HAART [21]. Another study on HIV/HCV co-infected patients reported decreased duration of survival from time to diagnosis of HIV infection and AIDS [22]. HIV/HCV co-infected veterans were at an increased risk of death due to co-infection even after controlling for exposure to HAART and response to HAART [23]. The Danish Cohort Study found a significantly increased overall mortality in addition to mortality from liver-related and AIDS-related causes in HIV/HCV co-infected [4] and HIV/HBV co-infected patients on HAART [5]. Another study also reported an increased frequency of deaths in HIV/HBV and HIV/HCV co-infected individuals [24]. HIV/HBV co-infected patients in a multicentre cohort study showed an increased mortality mainly attributed to liver disease in spite of being on HAART, in addition to an increased risk of AIDS-related death [25]. A meta-analysis on HIV/HBV co-infection reported a significant effect of co-infection on overall mortality, an association reported in studies conducted before and after starting HAART [26]. A similar meta-analysis on HIV/HCV co-infection found an increased risk for overall mortality in co-infected individuals during the HAART era [27].

Although these studies have reported an increased mortality in HIV-hepatitis co-infected individuals, other studies have noted no effect on mortality with co-infection or have attributed mortality to mostly liver-related causes. With the exception of a few studies [4, 5, 19, 20, 23], most studies had smaller sample sizes [9–11, 13, 17, 21, 22, 25], shorter duration of follow-up [9] and focused mainly on hospital- or clinic-based populations [8, 18, 22]. Therefore, the objectives of our study were to estimate the mortality and identify the factors associated with mortality in all HIV-hepatitis co-infected individuals in the state of Michigan using a statewide population-based surveillance system.

METHODS

A retrospective cohort design was utilized in which HIV/AIDS-infected individuals of all age groups residing in Michigan during the period 1 January 2006 to 31 December 2009 were matched to hepatitis B and hepatitis C cases from the same period [28]. The HIV/AIDS data were obtained from the enhanced HIV/AIDS Reporting System (eHARS) maintained by the HIV/STD/VH/TB Epidemiology Section whereas the hepatitis B and C data were obtained from the Michigan Disease Surveillance System maintained by the Surveillance and Infectious Disease Epidemiology Section of MDCH [28]. These datasets were linked together to enable matching of hepatitis B and C and HIV/AIDS cases to the same individual. The linkage was performed by a single employee using SAS software (SAS Institute Inc., USA) and utilized a two-step process involving first probabilistic, then deterministic linkages. Ultimately, broad linkages were made using last name soundex, first three letters of the last name, as well as year of birth. For those records linked, points were assigned based on exact match of all parts of name and date of birth, as well as sex and social security number if present. Those links scoring less than 100% on all matching variables were examined by hand to determine likeliness of sameness.

Ethical approval for the study was obtained from the institutional review board at Michigan State University and MDCH. To safeguard the privacy and confidentiality of the participants, an employee of the HIV/STD/VH/TB Epidemiology Section performed the record linkage. Health Insurance Portability and Accountability Act guidelines on public health information were followed to de-identify subjects included in the study. Information on a number of socio-demographic characteristics and

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laboratory tests of the HIV/AIDS-infected individuals was obtained. Independent variables included in the analysis were sex, race, age at HIV diagnosis, current HIV status (to December 2009), risk for transmission of HIV, and a binary indicator for co-infection. An HIV/AIDS individual was categorized as co-infected if he/she had been concurrently infected with confirmed HBV or HCV (acute and chronic) based on the Centres for Disease Control and Prevention (CDC) case definition [29] and residing in Michigan during the years 2006–2009. The rationale for creating the co-infection status variable was the fact that the three diseases share similar routes of transmission [30]. Any HIV/AIDS-infected individual who had a diagnosis of acute or chronic hepatitis B or C before 2006 was not included in the study. The HIV/AIDS case definition was based on the CDC's 1993 revised classification system of HIV [31].

Mortality was ascertained from vital records by using the entry date as 1 January 2006 when the study was started and 31 December 2010 the date used when the study was concluded. Only HIV/AIDS-hepatitis co-infected individuals that were diagnosed during 2006–2009 and HIV/AIDS not co-infected individuals were included in the analysis. To allow for additional time to follow-up, the study was concluded in 2010 (4 years follow-up). The duration of survival of the HIV/AIDS-hepatitis co-infected individuals as well as the HIV/AIDS not co-infected individuals was calculated from the time (number of days) spent in the study until the date of death. Those alive at the end of the study were considered censored.

The Kaplan–Meier method was utilized to construct survival curves for the co-infected and not co-infected groups. For comparison of survival curves the log rank test was used. Cox proportional hazards regression analysis was conducted to assess the association of variables with mortality and results summarized using hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs). All possible interactions were checked and entered into the final model based on statistical significance or biological plausibility. Statistical analyses were performed in SAS statistical software version 9.2 (SAS Institute Inc.).

Table 1. *Distribution of basic characteristics of the HIV/AIDS-infected individuals in Michigan (n = 13 930), 2006–2009*

Variable	Frequency (%)
Co-infection	
Co-infected*	572 (4·1)
Not co-infected	13 358 (95·9)
Sex	
Male	10 584 (76·0)
Female	3346 (24·0)
Race	
White(non-Hispanic)	4956 (35·6)
Black (non-Hispanic)	8088 (58·1)
Hispanic	569 (4·1)
Asian/HI/PI	72 (0·5)
American Indian/Alaskan Native (non-Hispanic)	42 (0·3)
Multi race/Unknown/Other (non-Hispanic)	203 (1·4)
HIV transmission risk†	
Blood products	85 (0·6)
High-risk heterosexual	1796 (12·9)
Presumed heterosexual – male	1201 (8·6)
Presumed heterosexual – female	793 (5·7)
IDU	1362 (9·8)
MSM	6807 (48·9)
MSM/IDU	539 (3·9)
Perinatal	156 (1·1)
Unknown	1191 (8·5)
Age at HIV diagnosis (years)	
0–12	178 (1·3)
13–19	638 (4·6)
20–24	1753 (12·6)
25–29	2260 (16·2)
30–39	4833 (34·7)
40–49	2974 (21·3)
50–59	1044 (7·5)
⩾60	247 (1·8)
Missing	3 (0·0)
Current HIV status	
AIDS	7707 (55·3)
HIV-NA (not AIDS)	6223 (44·7)

Asian/HI/PI, Asian/Hawaiian/Pacific Islander, non-Hispanic; MSM, men who have sex with men; IDU, injecting drug use.

* Co-infection = any HIV-infected individual that is infected by hepatitis B and C virus (acute and chronic).

† Heterosexual female = female who denies IDU and has had sex with a man.

RESULTS

The total number of individuals infected with HIV/AIDS during the study period was13 930. The prevalence of HIV-hepatitis co-infection in these individuals was 4·1% (Table 1) with chronic hepatitis B in 1·8% and chronic hepatitis C in 2·2% (data not shown). There were proportionately more males (76%) infected with HIV/AIDS compared to

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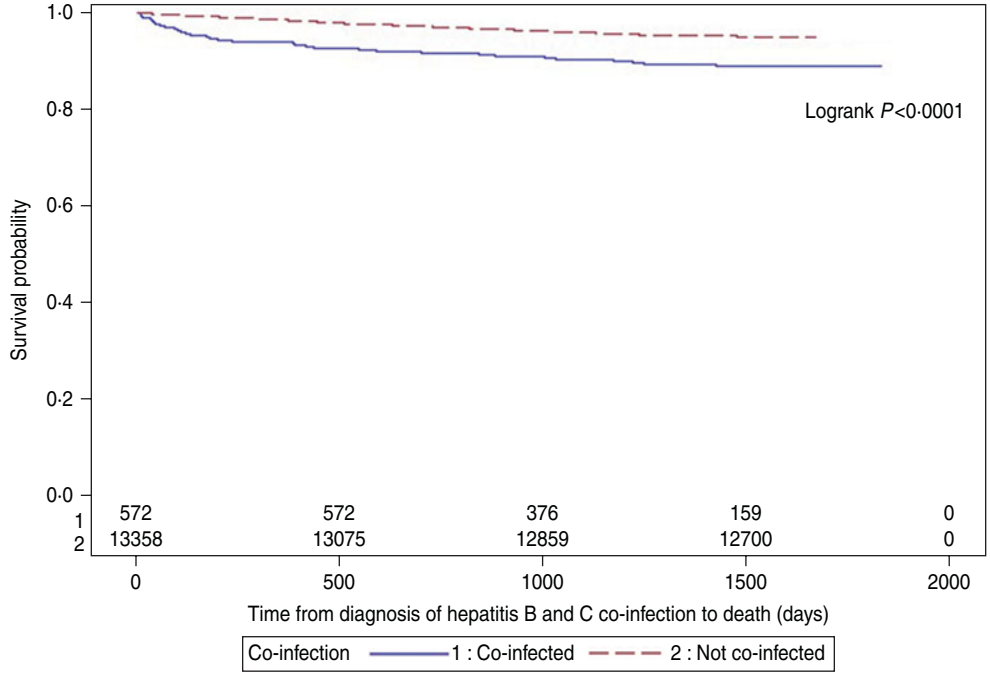

Fig. 1. [*colour online*]. Kaplan–Meier curves showing mortality in HIV/AIDS-infected individuals, stratified by co-infection status.

females (24%). The race/ethnicity distribution was black (58·1%), white (35·6%), Hispanic (4·1%), multiracial (1·4%), Asian/Hawaiian/Pacific Islander (0·5%), and American Indian/Alaskan Native (0·3%). In HIV transmission risk categories, HIV/AIDS-infected individuals were predominantly men who have sex with men (MSM) (48·9%) followed by high-risk heterosexual (HRH) (12·9%), IDU (9·8%), heterosexual male (8·6%), unknown risk (8·5%), heterosexual female (5·7%), MSM/IDU (3·9%), perinatal (1·1%) and blood products (0·6%). With respect to age at HIV diagnosis, the distribution was: 30–39 years (34·7%), 40–49 years (21·3%), 25–29 years (16·2%), and 20–24 years (12·6%). There were more individuals with AIDS (55·3%) compared to HIV only (44·7%).

A total of 727 HIV/AIDS-infected individuals died during the follow-up period. The total number of deaths was proportionately more in hepatitis co-infected individuals (10%) as compared to not co-infected individuals (5%) (data not shown). Survival in the HIV-hepatitis co-infected group was significantly lower compared to the not co-infected group (log rank test P value <0·0001, Fig. 1). HIV transmission risk was categorized as blood products, heterosexual, IDU, MSM/IDU, MSM, perinatal and undetermined (Table 2) [32]. Race was categorized as black, white, Hispanic and other and age at HIV diagnosis was reclassified into age groups <20, 20–29, 30–39, 40–49, and ⩾50 years [6]. From univariable Cox regression analysis, co-infected individuals had a decreased survival (HR 2·4, 95% CI 1·8–3·2) compared to not co-infected individuals. Females compared to males had an increased mortality (HR 1·2, 95% CI 1·0–1·4). Compared to white race the mortality risk was higher in blacks (HR 1·5, 95% CI 1·3–1·8) and individuals belonging to the other race category (HR 2·3, 95% CI 1·5–3·4) (Table 2). For age at HIV diagnosis, a gradual increase in mortality with increasing age was observed, and individuals who were aged ⩾50 years had the shortest survival (HR 9·0, 95% CI 5·0–16·1). Individuals currently with AIDS showed a decreased survival compared to only HIV-infected individuals (Table 2). For HIV transmission risk categories, IDU had a decreased survival (HR 2·8, 95% CI 2·3–3·4) followed by MSM/IDU (HR 1·8, 95% CI 1·2–2·5), individuals with undetermined risk (HR 1·7, 95% CI 1·4–2·1) and, heterosexual practices (HR 1·4, 95% CI 1·2–1·8).

Variable selection for the adjusted model was based upon statistical significance of the variables from the univariable analysis and biological plausibility. In the final model, individuals of other and black race had decreased survival compared to white race adjusting for all other variables in the model

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Table 2. *Multivariable Cox regression analysis of factors associated with survival in HIV/AIDS-infected individuals in Michigan, 2006–2009*

Variable	Crude HR	95% CI	Adjusted HR	95% CI
Co-infection				
Not co-infected	1			
Co-infected	2·4	(1·8–3·2)		
Sex				
Male	1		1	
Female	1·2	(1·0–1·4)	0·9	(0·8–1·2)
Race				
White (non-Hispanic)	1		1	
Black (non-Hispanic)	1·5	(1·3–1·8)	1·3	(1·1–1·6)
Hispanic	1·1	(0·7–1·7)	1·0	(0·6–1·5)
Other*	2·3	(1·5–3·4)	2·2	(1·4–3·2)
Age at HIV diagnosis (years)				
<20	1		1	
20–29	2·4	(1·3–4·4)	1·7	(0·9–3·1)
30–39	3·1	(1·8–5·6)	1·8	(1·0–3·3)
40–49	4·6	(2·6–8·2)	2·5	(1·4–4·5)
⩾50	9·0	(5·0–16·1)	4·7	(2·6–8·6)
Current HIV status				
HIV-NA (not AIDS)	1			
AIDS	5·9	(4·8–7·4)		
HIV transmission risk				
MSM	1		1	
Blood products	1·3	(0·5–3·5)	1·4	(0·5–3·7)
Heterosexual†	1·4	(1·2–1·8)	1·4	(1·1–1·8)
IDU	2·8	(2·3–3·4)	2·1	(1·6–2·6)
MSM/IDU	1·8	(1·2–2·5)	1·5	(1·1–2·2)
Perinatal‡	—	—	—	—
Undetermined§	1·7	(1·4–2·1)	1·5	(1·2–1·9)
Interaction				
Current HIV status × co-infection				
AIDS *vs* HIV-NA				
Co-infected			2·4	(1·2–4·8)
Not co-infected			5·9	(4·6–7·4)

HR, Hazard ratio; CI, confidence interval; MSM, men who have sex with men; IDU, injecting drug use.
* Other = Multiracial, Asian, Hawaiian & Pacific Islander, Alaskan Native, American Indian.
† Heterosexual = presumed heterosexual female and high-risk heterosexual.
‡ Some cells have zero counts.
§ Undetermined = unknown (males and females with no identified risk) and presumed heterosexual male.

(Table 2). Age at HIV diagnosis showed an increased mortality with increasing age after adjustment. Similarly, IDU, MSM/IDU, individuals with undetermined risk and, heterosexual practices had decreased survival compared to MSM after adjusting for all other variables in the model (Table 2). The final model also included an interaction between current HIV status and co-infection status which indicates that the effect of having AIDS compared to HIV only differs if the individual is co-infected (HR 2·4, 95% CI 1·2–4·8) or not co-infected (HR 5·9, 95% CI 4·6–7·4) in relation to mortality (Table 2). (Separate univariable and multivariable analysis for HIV/HCV and HIV/HBV co-infected individuals are shown in Supplementary Tables 1 and 2).

DISCUSSION

In this study, mortality in HIV-hepatitis B and C co-infected individuals was nearly twice that of HIV-infected individuals without the co-infections. Being co-infected with either HCV or HBV resulted

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in an increased risk for mortality [4, 18–27]. However, there were no liver-related deaths recorded in the cohort during the follow-up period. Conceivably, there may be factors other than liver disease or treatment-related hepatotoxicity that might lead to this increased risk of mortality. As identified by an earlier study, HIV/HCV co-infected patients were less likely to receive HAART than non-HCV-infected patients [22]. It is plausible that increased mortality in HIV/HCV co-infected individuals is causing the decreased use of HAART. A study on siblings of HIV/HCV co-infected patients reported a higher mortality in these patients compared to siblings of only HIV-infected patients or siblings of control subjects [33]. This excess mortality was attributed to probable differences in family background and socioeconomic factors like shared socioeconomic disadvantage or family history of IDU. Another study revealed an increased mortality in siblings of HIV/HCV co-infected patients to be related to substance abuse, mainly alcohol or drug abuse [34]. Other factors like lack of access to care, treatment non-compliance, alcohol- or drug-related morbidity or postponement of treatment for co-infection due to physician's fears of hepatotoxicity could also play an important role in the increased mortality in co-infected individuals.

A study in Brazil attributed the higher mortality in AIDS-HCV co-infected cases to the receipt of less antiretroviral therapy (ART) in these patients [35]. This discrepancy in treatment could be due to physicians' knowledge that HAART may be hepatotoxic, inability of patients to tolerate ART or physicians' belief's that IDUs are non-compliant [35]. HIV/HCV co-infection might also be a proxy for some other types of high-risk behaviours that lead to an increased mortality from non-AIDS-related causes in co-infected individuals [36].

Females were also found to have an increased mortality. A study focusing on gender differences in HIV/HCV co-infected patients on HAART identified females as having reduced survival compared to males [37]. However, this association did not remain significant after adjustment in our study. An increased mortality was observed in individuals of black and other race as compared to white race. A lower interferon-alpha response resulting in a slower viral decline has been observed in HIV/HCV co-infected blacks [38], which could be contributing to the decreased survival noted in our study. However, an even higher mortality was observed in individuals belonging to other races which included multiracial groups. Plausibly, there might be certain high-risk behaviours or practices that put these populations at increased risk for mortality. It is also possible that some of the populations in the other race group include individuals coming from countries which have decreased immunization rates or unsafe injection practices. This finding needs to be explored further to identify such practices or behaviours.

A gradual increase in mortality was observed with increasing age and individuals diagnosed with HIV at age $\geqslant 50$ years had the highest predisposition for mortality [22, 23]. Individuals currently having AIDS had a decreased survival compared to HIV-only-infected individuals [4, 11, 39]. A higher propensity for mortality was also observed in IDUs followed by MSM/IDUs, individuals with undetermined risk and heterosexuals. IDU has been identified as a major contributor to mortality [19, 20]. Non-compliance to treatment in IDUs could be a factor as well as physicians' belief that IDUs are non-compliant. Other factors related to IDU or pharmacological interactions between illicit drugs and ART could have led to the decreased survival as well. It is noteworthy that the effect of IDU was apparent in the category of MSM who also have history of IDU. This observation indicates that MSM who are already vulnerable to developing HIV or AIDS have additional risk if they are in the practice of injecting drugs.

The final adjusted model showed a significantly increased mortality; in HIV-infected individuals belonging to black and other races, older age at HIV diagnosis, IDUs, MSM/IDUs, individuals with undetermined risk and heterosexuals as well as a significant interaction between current HIV status and co-infection. To our knowledge, this is the first study that documents an interaction between current HIV status and co-infection. Based on these results, individuals who currently have AIDS and are not co-infected are at a significantly decreased survival compared to individuals having AIDS who are co-infected. It is possible that individuals who are diagnosed with AIDS and are not co-infected do not get the extra care and treatment that may be given to AIDS patients who are co-infected with hepatitis viruses. It is also likely that these individuals tend to die earlier before they become infected with hepatitis viruses. Additionally, AIDS-hepatitis co-infected individuals may be diagnosed earlier because of the co-morbidity and are then put on appropriate therapy for co-infection which increases their duration of

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survival. Moreover, in another study of HIV/HCV-infected individuals, HAART decreased the mortality rate in HIV/HCV co-infected individuals [40]. This could partially explain the relatively decreased, albeit significant, risk observed in AIDS-infected individuals with co-infection.

We were not able to obtain complete information on ART in HIV/AIDS-infected individuals. However, a subset analysis of HIV/AIDS-infected individuals who were on therapy yielded similar results as our multivariate analysis (Supplementary Table S3). Tests for CD4 counts were not routinely done on all HIV cases which restricted our analysis. Nevertheless, analysis of data containing CD4 counts in this cohort did not identify any association between CD4 counts and mortality. Furthermore, due to passive reporting of hepatitis cases, there may be underreporting and under-detection of these cases. The Michigan HIV surveillance system includes data only for persons who have been confidentially reported by name which could lead to underreporting of cases [6]. Another limitation of the surveillance system is that the data on ART agents, HIV load, time of development of AIDS and the underlying causes of death are not routinely collected which could have been used in our analysis.

However, the strength of our study is its population base which includes all the statewide data detected by the surveillance system on almost all HIV/AIDS-infected individuals as well as persons having hepatitis B and C co-infection residing in Michigan. Our study also had a relatively sufficient follow-up period of 4 years, an adequate sample size, along with a representative group of persons including minorities with HIV infection.

With the advent of HAART, there has been an increased survival in HIV/AIDS patients; however, challenges for treatment still remain because of co-morbidities like HBV and HCV infection. Our results indicate that mortality in HIV/AIDS and hepatitis co-infected individuals is a continuing problem even after the availability of HAART. Our study identified certain high-risk populations like individuals of black and other race and IDUs as well as older age at HIV diagnosis as a higher risk for mortality. Currently having AIDS conferred a higher risk of mortality highlighting the importance of early diagnosis and treatment of AIDS.

Our study also demonstrated an interaction between current HIV status and co-infection, a finding which underscores the importance of complex relationships between different factors associated with mortality. Further exploration of these associations is needed in order to plan and implement interventions to reduce mortality in this vulnerable population. Future research should focus upon the impact of early initiation of ART for HIV co-infected individuals, advantages of early screening of all HIV/AIDS-infected individuals for co-morbidities and identification of additional high-risk behaviours or practices that may be present specifically in co-infected individuals.

SUPPLEMENTARY MATERIAL

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0950268813003038.

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DECLARATION OF INTEREST

None.

REFERENCES

1. **UNAIDS.** Global Report. UNAIDS report on the Global AIDS Epidemic 2010 (http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2010/20101123_globalreport_en.pdf). Accessed January 24 2010.
2. **UNAIDS.** United States of America. HIV and AIDS estimates 2009 (http://www.unaids.org/en/regionscountries/countries/unitedstatesofamerica/). Accessed 24 January 2010.
3. **Michigan Department of Community Health.** Quarterly HIV/AIDS report, Michigan. January 2011 (http://www.michigan.gov/documents/mdch/Jan_2011_344131_7.pdf). Accessed 24 February 2011.
4. **Weis N, *et al.*** Impact of hepatitis C virus coinfection on response to highly active antiretroviral therapy and outcome in HIV-infected individuals: a nationwide cohort study. *Clinical Infectious Diseases* 2006; **42**: 1481–1487.
5. **Omland LH, *et al.*** Impact of hepatitis B virus co-infection on response to highly active antiretroviral treatment and outcome in HIV-infected individuals: a

nationwide cohort study. *HIV Medicine* 2008; **9**: 300–306.

6. **Michigan Department of Community Health.** 2010 Epidemiologic Profile of HIV/AIDS in Michigan (http://www.michigan.gov/documents/mdch/2010_EPI_PROFILE_ENTIRE_335483_7.pdf). Accessed January 24 2010.
7. **Sabin CA, *et al.*** The association between hepatitis C virus genotype and human immunodeficiency virus disease progression in a cohort of hemophilic men. *Journal of Infectious Disease* 1997; **175**: 164–168.
8. **Sulkowski MS, *et al.*** Hepatitis C and progression of HIV disease. *Journal of the American Medical Association* 2002; **288**: 199–206.
9. **Hoffmann CJ, *et al.*** Hepatitis B virus infection and response to antiretroviral therapy (ART) in a South African ART program. *Clinical Infectious Diseases* 2008; **47**: 1479–1485.
10. **Riley ED, *et al.*** Antiretroviral therapy, hepatitis C virus, and AIDS mortality among San Francisco's homeless and marginally housed. *Journal of Acquired Immune Deficiency Syndrome* 2005; **38**: 191–195.
11. **Macías J, *et al.*** Influence of hepatitis C virus infection on the mortality of antiretroviral-treated patients with HIV disease. *European Journal of Clinical Microbiology and Infectious Diseases* 1998; **17**: 167–170.
12. **Sherman KE, *et al.*** Hepatitis C virus prevalence among patients infected with human immunodeficiency virus: a cross-sectional analysis of the US adult AIDS Clinical Trials Group. *Clinical Infectious Diseases*. 2002; **34**: 831–837.
13. **Sulkowski MS, Thomas DL.** Hepatitis C in the HIV-infected person. *Annals of Internal Medicine* 2003; **138**: 197–207.
14. **Thomas DL.** Hepatitis C and human immunodeficiency virus infection. *Hepatology* 2002; **36**: 201–209.
15. **Thio CL, *et al.*** HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). *Lancet* 2002; **360**: 1921–1926.
16. **Bonacini M, *et al.*** Survival in patients with HIV infection and viral hepatitis B or C: a cohort study. *AIDS* 2004; **18**: 2039–2045.
17. **Konopnicki D, *et al.*** Hepatitis B and HIV: prevalence, AIDS progression, response to highly active antiretroviral therapy and increased mortality in the EuroSIDA cohort. *AIDS* 2005; **19**: 593–601.
18. **Ockenga J, *et al.*** Hepatitis B and C in HIV-infected patients. Prevalence and prognostic value. *Journal of Hepatology* 1997; **27**: 18–24.
19. **Greub G, *et al.*** Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus coinfection: the Swiss HIV Cohort Study. *Lancet* 2000; **356**: 1800–1805.
20. **Voirin N, *et al.*** Survival in HIV-infected patients is associated with hepatitis C virus infection and injecting drug use since the use of highly active antiretroviral therapy in the Lyon observational database. *Journal of Viral Hepatitis* 2004; **11**: 559–562.
21. **Sheng WH, *et al.*** Impact of chronic hepatitis B virus (HBV) infection on outcomes of patients infected with HIV in an area where HBV infection is hyperendemic. *Clinical Infectious Diseases* 2004; **38**: 1471–1477.
22. **Anderson KB, Guest JL, Rimland D.** Hepatitis C virus coinfection increases mortality in HIV-infected patients in the highly active antiretroviral therapy era: data from the HIV Atlanta VA Cohort Study. *Clinical Infectious Diseases* 2004; **39**: 1507–1513.
23. **Backus LI, *et al.*** Effects of hepatitis C virus coinfection on survival in veterans with HIV treated with highly active antiretroviral therapy. *Journal of Acquired Immune Deficiency Syndrome* 2005; **39**: 613–619.
24. **Marcellin P, *et al.*** Mortality related to chronic hepatitis B and chronic hepatitis C in France: evidence for the role of HIV coinfection and alcohol consumption. *Journal of Hepatology* 2008; **48**: 200–207.
25. **Hoffmann CJ, *et al.*** Hepatitis B and long-term HIV outcomes in coinfected HAART recipients. *AIDS* 2009; **23**: 1881–1889.
26. **Nikolopoulos GK, *et al.*** Impact of hepatitis B virus infection on the progression of AIDS and mortality in HIV-infected individuals: a cohort study and meta-analysis. *Clinical Infectious Diseases* 2009; **48**: 1763–1771.
27. **Chen TY, *et al.*** Meta-analysis: increased mortality associated with hepatitis C in HIV-infected persons is unrelated to HIV disease progression. *Clinical Infectious Diseases* 2009; **49**: 1605–1615.
28. **Butt ZA, *et al.*** Hepatitis B and C co-infection in HIV/AIDS population in the state of Michigan. *Epidemiology and Infection*. Published online: 12 March 2013. doi: 10.1017/S0950268813000538.
29. **CDC.** 2012 Nationally notifiable diseases and conditions and current case definitions (http://stacks.cdc.gov/view/cdc/12088). Accessed 20 November 2013.
30. **Kim JH, *et al.*** Co-infection of hepatitis B and hepatitis C virus in human immunodeficiency virus-infected patients in New York City, United States. *World Journal of Gastroenterology* 2008; **14**: 6689–6693.
31. **Anon.** 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *Morbidity and Mortality Weekly Report. Recommendations and Report* 1992; **41**: 1–19.
32. **Michigan Department of Community Health.** Quarterly HIV/AIDS report, Michigan, October 2010 (http://www.michigan.gov/documents/mdch/Oct_2010_335648_7.pdf). Accessed 2 January 2011.
33. **Hansen AB, *et al.*** Mortality in siblings of patients coinfected with HIV and hepatitis C virus. *Journal of Infectious Diseases* 2007; **195**: 230–235.
34. **Hansen AB, *et al.*** Cause-specific excess mortality in siblings of patients co-infected with HIV and hepatitis C virus. *PLoS One* 2007; **2**: e738.
35. **Marins JR, *et al.*** Characteristics and survival of AIDS patients with hepatitis C: the Brazilian National Cohort of 1995–1996. *AIDS* 2005; **19**: 27–30.
36. **Jain MK.** Mortality in patients coinfected with hepatitis B virus and HIV: could antiretroviral therapy make a difference? *Clinical Infectious Diseases* 2009; **48**: 1772–1774.

37. **Emery J, *et al.*** Gender differences in clinical, immunological, and virological outcomes in highly active antiretroviral-treated HIV-HCV coinfected patients. *Patient Preference and Adherence* 2010; **4**: 97–103.
38. **Rozenberg L, *et al.*** Therapeutic response to peg-IFN-alpha-2b and ribavirin in HIV/HCV co-infected African-American and Caucasian patients as a function of HCV viral kinetics and interferon pharmacodynamics. *AIDS* 2009; **23**: 2439–2450.
39. **Rosenthal E, *et al.*** Mortality due to hepatitis C-related liver disease in HIV-infected patients in France (Mortavic 2001 study). *AIDS* 2003; **17**: 1803–1809.
40. **Tedaldi EM, *et al.*** Influence of coinfection with hepatitis C virus on morbidity and mortality due to human immunodeficiency virus infection in the era of highly active antiretroviral therapy. *Clinical Infectious Diseases* 2003; **36**: 363–367.