Prevalence and burden of HCV co-infection in people living with HIV: a global systematic review and meta-analysis

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Summary

Background At global level, there are 37 million people infected with HIV and 115 million people with antibodies to hepatitis C virus (HCV). Little is known about the extent of HIV–HCV co-infection. We sought to characterise the epidemiology and burden of HCV co-infection in people living with HIV.

Methods In this systematic review and meta-analysis we searched MEDLINE, Embase, CINAHL+, POPLINE, Africa-wide Information, Global Health, Web of Science, and the Cochrane Library and WHO databases for studies measuring prevalence of HCV and HIV, published between Jan 1, 2002, and Jan 28, 2015. We included studies in HIV population samples of more than 50 individuals and recruited patients based on HIV infection status or other behavioural characteristics. We excluded editorials or reviews containing no primary data, samples of HCV or HIV–HCV co-infected individuals, or samples relying on self-reported infection status. We also excluded samples drawn from populations with other comorbidities or undergoing interventions that put them at increased risk of co-infection. Populations were categorised according to HIV exposure, with the regional burden of co-infection being derived by applying co-infection prevalence estimates to published numbers of HIV-infected individuals. We did a meta-analysis to estimate the odds of HCV in HIV-infected individuals compared with their HIV-negative counterparts.

Findings From 31767 citations identified, 783 studies met the inclusion criteria, resulting in 902 estimates of the prevalence of HIV–HCV co-infection. In HIV-infected individuals, HIV–HCV co-infection was 2·4% (IQR 0·8–5·8) within general population samples, 4·0% (1·2–8·4) within pregnant or heterosexually exposed samples, 6·4% (3·2–10·0) in men who have sex with men (MSM), and 82·4% (55·2–88·5) in people who inject drugs (PWID). Odds of HCV infection were six times higher in people living with HIV (5·8, 95% CI 4·5–7·4) than their HIV-negative counterparts. Worldwide, there are approximately 2278400 HIV–HCV co-infections (IQR 1271300—4417000) of which 1362700 (847700–1381800) are in PWID, equalling an overall co-infection prevalence in HIV-infected individuals of 6·2% (3·4–11·9).

Interpretation We noted a consistently higher HCV prevalence in HIV-infected individuals than HIV-negative individuals across all risk groups and regions, but especially in PWID. This study highlights the importance of routine HCV testing in all HIV-infected individuals, but especially in PWID. There is also a need to improve country-level surveillance of HCV prevalence across different population groups in all regions.

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Introduction

HIV and hepatitis C virus (HCV) infection are major global public health concerns, with overlapping modes of transmission and affected populations. As of December, 2014, an estimated 36·9 million people were living with HIV, 2 million were newly infected, and 1·6 million died.[1] Although HIV transmission has declined since 2001, with improved survival due to the scale-up of antiretroviral therapies (ART), more people are living with HIV than ever before.[2] In 2005, more than 184 million people were estimated to be HCV antibody positive.[3] Data from 2014 suggest that this number has declined to 115 million (range 92–149)[4] as a result of improved screening of blood supply, decreases in injecting risk behaviours, and differences in prevalence reported from southeast Asia. However, other evidence[5,6] suggests that the disease burden is high, with 3–4 million new infections and 704000 deaths in 2013.[3,7] HCV treatment has been transformed with the advent of direct-acting antivirals, which offer high cure rates within 12–24 weeks.[8]

The interaction between HIV and HCV co-infection affects the transmission and natural history of HCV infection. The transmission efficiency of HCV increases in the presence of HIV infection, with the perinatal transmission risk doubling in HIV-infected mothers.[9,10] People living with HIV without treatment are less likely to spontaneously clear HCV infection, have higher HCV viral loads, and experience more rapid HCV disease progression than those without HIV infection.[11] Although ART improves outcomes in HCV co-infected patients, with decreased HCV-related mortality,[12] HCV co-infection might also complicate HIV treatment, with some evidence suggesting an increased risk of drug-related hepatoxicity in those receiving ART.[12] An absence of consistent data remains for the effect of HCV co-infection on HIV progression.[9,12,13]

Research in context

Evidence before this study

In this systematic review and meta-analysis we searched eight databases for studies that reported the prevalence of HCV and HIV, published between Jan 01, 2002, and Jan 28, 2015, following PRISMA guidelines. The searches were done with no language restrictions on Jan 28, 2015, in MEDLINE, Embase, CINAHL+, POPLINE, Africa-wide Information, Global Health, Web of Science, and the Cochrane Library, Index Medicus of the Eastern Mediterranean Region, Index Medicus of the South-East Asian Region, LILACS, and Western Pacific Region Index Medicus. Search terms included "HIV OR Human immunodeficiency virus", "OR Hepatitis-C OR HCV", and "prevalen* OR inciden* OR seroprevalen* OR screening OR surveillance OR population* OR survey* OR epidem* OR data collection OR population sample* OR community survey* OR cohort OR cross-sectional OR longitude* OR follow-up". Searches were tailored to each database. Reference lists were screened for additional sources.

We included studies with estimates of HCV co-infection in HIV population samples of more than 50 individuals recruited based on HIV infection status or other behavioural characteristic. We excluded editorials or reviews containing no primary data, no samples of HCV or HIV–HCV-infected individuals, or samples relying on self-reported infection status. We excluded samples drawn from populations with other comorbidities or undergoing interventions that put them at increased risk of co-infection. The search focused on published medical literature and did not include an exhaustive review of grey literature.

Previous reviews of HIV–HCV co-infection have focused on specific regions or sub-populations or have not used systematic review methods to extract and synthesise data. Data are needed to establish the global burden of HCV co-infection in HIV-infected individuals and to identify the populations at risk

and the key geographical regions most affected. These data are essential to inform normative guidance and service delivery for testing and care and treatment services.

Added value of study

We estimate a midpoint of roughly 2·3 million (IQR 1·3–4·3 million) cases of HIV–HCV co-infection worldwide, of whom more than half (an estimated 1·3 million [0·89–1·4 million]) are PWID. This number equates to a worldwide HCV co-infection prevalence of 6·2% (3·4–11·9) in HIV-infected individuals. The greatest burden of HIV–HCV co-infection is in eastern Europe, where an estimated 607 700 HIV-infected people are co-infected with HCV, followed by 429 600 people in sub-Saharan Africa. Prevalence of HCV co-infection in HIV-infected people is highest in PWID (82·4%, 55·2–88·5), followed by MSM (6·4%, 3·2–10·0) and pregnant or heterosexually exposed populations (4·0%, 1·2–8·4), and lowest in general population samples (2·4%, 0·8–5·8). Odds of HCV infection are six times higher in HIV-infected people than in HIV-negative populations ranging from 1·6 times higher in the general population, 1·4–6·8 times higher in sex workers, and 4–13 times higher in MSM, PWID, and high-risk populations.

Implications of all the available evidence

Our findings clearly show that HIV-infected individuals are at high risk of HCV infection, particularly PWID who constitute 58% of the global burden of HCV co-infections in HIV-infected individuals. Routine testing of HCV in HIV-infected individuals is needed, including good linkage to care and treatment in PWID and MSM especially.

There is also a need to improve surveillance and country-level data on prevalence of HCV in all populations to help countries define their epidemiology and inform policies for hepatitis C testing, prevention, and care and treatment services.
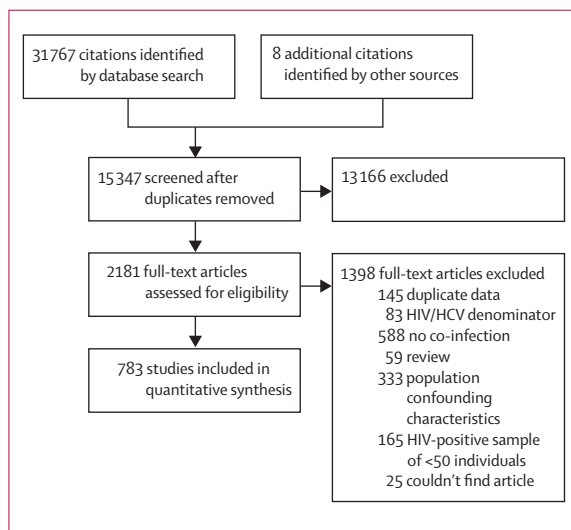
Figure 1: Flow chart of included studies

As people living with HIV live longer, HCV-related liver disease in co-infected patients is becoming a major cause of morbidity and mortality. However, the burden of HIV–HCV co-infection is poorly understood. One review[14] suggested that 4–5 million HIV-infected individuals are infected with HCV, but it relied on a small number of studies and unclear methods, whereas a second review[15] reported prevalence from selected studies only. Other reviews have provided estimates for sub-Saharan Africa only[16,17] or in people who inject drugs (PWID),[18] but there have been no reviews documenting the global burden of HCV co-infection in HIV-infected individuals. Reliable estimates are needed to establish the scale of the public health problem posed by HCV co-infection and to inform regional and national strategies for hepatitis screening and management.[19–23] We therefore undertook a systematic review to estimate the prevalence and global burden of HCV antibody seropositivity in HIV-infected individuals.

	General population						Heterosexual or pregnant HIV-infected individual						PWID						MSM					
	Total studies		Best estimate				Total studies		Best estimate				Total studies		Best estimate				Total studies		Best estimate			
	n	Range*	%	Score	n	Year	n	Range*	%	Score†	n	Year	n	Range*	%	Score†	n	Year	n	Range*	%	Score	n	Year
West and central Africa																								
Burkina Faso	5	4·8–14·0	9·6%	B3	761	2010	··	··	··	··	··	··	··	··	··	··	··	··	··	··	··	··	··	··
Cameroon	··	··	··	··	··	··	2	9·0–12·4	12·4%	C2	169	2003	··	··	··	··	··	··	··	··	··	··	··	··
Congo	··	··	··	··	··	··	1	10·0	10·0%	B2	209	2008	··	··	··	··	··	··	··	··	··	··	··	··
The Gambia	··	··	··	··	··	··	1	11·0	11·0%	C0	572	2009	··	··	··	··	··	··	··	··	··	··	··	··
Ghana	2	0·0–3·6	3·6%	B2	168	2012	··	··	··	B2	··	··	··	··	··	··	··	··	··	··	··	··	··	··
Mali	··	··	··	··	··	··	1	8·0	8·0%	B2	242	2004	··	··	··	··	··	··	··	··	··	··	··	··
Nigeria	4	2·0–15·0	2·4%	C2	83	2009	13§	0·7–22·0	0·7%	C1	404	2012	··	··	··	··	··	··	··	··	··	··	··	··
Senegal	··	··	··	··	··	··	1	8·0	8·0%	C2	363	2002	··	··	··	··	··	··	··	··	··	··	··	··
Total‡	11	2·4–9·6	3·6%	··	··	··	19	8–11·0	9·0%	··	··	··	··	··	··	··	··	··	··	··	··	··	··	··
Southern Africa																								
Botswana	··	··	··	··	··	··	1	0·0	0·0%	B2	1995	2006	··	··	··	··	··	··	··	··	··	··	··	··
Lesotho	··	··	··	··	··	··	1	0·5	0·5%	B2	205	2007	··	··	··	··	··	··	··	··	··	··	··	··
South Africa	··	··	··	··	··	··	1	1·0	1·0%	C2	300	2009	··	··	··	··	··	··	··	··	··	··	··	··
Total‡	··	··	··	··	··	··	3	0–1·0	0·5%	··	··	··	··	··	··	··	··	··	··	··	··	··	··	··
East Africa																								
Comoros	··	··	··	··	··	··	1	4·0	4·0%	C0	50	2002	··	··	··	··	··	··	··	··	··	··	··	··
Djibouti	1	1·1	1·1%	C3	175	2000	··	··	··	··	··	··	··	··	··	··	··	··	··	··	··	··	··	··
Ethiopia	3	0·0–10·5	0·0%	C2	129	2010	8	1·3–10·5	3·6%	B2	500	2013	··	··	··	··	··	··	··	··	··	··	··	··
Kenya	··	··	··	··	··	··	1	1·1	1·1%	B2	378	2007	··	··	··	··	··	··	··	··	··	··	··	··
Malawi	··	··	··	··	··	··	3§	0·1–12·7	0·1%	B3	2041	2011	··	··	··	··	··	··	··	··	··	··	··	··
Mauritius	··	··	··	··	··	··	··	··	··	··	··	··	··	99·6	99·6%	B2	230	2009	··	··	··	··	··	··
Mozambique	1	1·4	1·4%	C3	217	2004	··	··	··	··	··	··	··	··	··	··	··	··	··	··	··	··	··	··
Rwanda	··	··	··	··	··	··	1	4·9	4·9%	C3	89	2004	··	··	··	··	··	··	··	··	··	··	··	··
Uganda	··	··	··	··	··	··	3§	0·4–3·3	0·4%	C0	4775	2011	··	··	··	··	··	··	··	··	··	··	··	··
Tanzania	1	0·0	0·0%	C2	60	2005	1	0·6	0·6%	C0	17539	2011	··	48·3	48·3%	B1	93	2011	1	38·5	38·5%	B0	65	2007
Zambia	··	··	··	··	··	··	1	1·2	1·2%	C2	323	2008	··	··	··	··	··	··	··	··	··	··	··	··
Total‡	6	0–1·3	0·6%	··	··	··	19	0·5–3·8	1·1%	··	··	··	··	48·3–99·6	73·9%	··	··	··	1	38·5	38·5%	··	··	··
South America																								
Argentina	··	··	··	··	··	··	1	21·0	21·0%	C0	357	2008	··	88·3	88·3%	B2	77	2001	2	0–29·1	29·1%	B0	85	2009
Brazil	1	7·0	7·0%	C3	2865	2006	3§	5·6–15·5	8·1%	C2	63	2010	··	21·0–82·4	82·4%	B2	205	2003	1	6	6·0%	B0	2307	2008
Chile	··	··	··	··	··	··	··	··	··	··	··	··	··	··	··	··	··	··	1	2·6	2·6%	B0	395	2007
Colombia	1	0·8	0·8%	C3	247	2009	··	··	··	··	··	··	··	··	··	··	··	··	··	··	··	··	··	··
Peru	··	··	··	··	··	··	··	··	··	··	··	··	··	··	··	··	··	··	1	0	16·0%	C3	162	2003

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	General population						Heterosexual or pregnant HIV-infected individual						PWID						MSM					
	Total studies		Best estimate				Total studies		Best estimate				Total studies		Best estimate				Total studies		Best estimate			
	n	Range*	%	Score	n	Year	n	Range*	%	Score†	n	Year	n	Range*	%	Score†	n	Year	n	Range*	%	Score	n	Year
(Continued from previous page)																								
Venezuela	..	..	..	..	..	..	2	0.7–15.4	0.7%	C3	418	2008	..	..	..	..	..	..	..	..	..	..	..	..
Total‡	2	0.8–7.0	3.9%	..	..	..	6	0.7–21.0	8.1%	..	..	..	..	82.4–88.3	85.5%	B0	..	..	5	4.3–22.5	11.0%	..	..	..
Caribbean																								
Puerto Rico	..	..	..	..	..	..	..	..	..	..	..	..	2	24.2–92.2	24.2%	B0	1308	2005	..	..	..	..	..	..
Total‡	..	..	..	..	..	..	..	..	..	..	..	..	2	24.2–92.2	24.2%	..	..	..	..	..	..	..	..	..
North America																								
Canada	..	..	..	..	..	..	2	4.3–9.8	4.3%	C0	94	2009	6	82.4–95.4	82.3%	B0	170	2010	3	11.8–26.0	17.3%	C0	208	2009
USA	..	..	..	..	..	..	8§	3.8–29.4	8.0%	B0	243	2011	13	8.0–94.7	83.5%	B3	158	2012	132	0.6–15.7	15.7%	B0	92	2011
Total‡	..	..	..	..	..	..	10	4.3–8.0	6.0%	..	..	..	19	82.5–83.5	82.9%	..	..	..	1656	15.7–17.3	16.2%	..	..	..
South and southeast Asia																								
Cambodia	..	..	..	..	..	..	1	5.3	5.3%	B3	3089	2012	..	..	..	..	..	..	..	..	..	..	..	..
India	8	0–29.4	0.0%	B3	91	2013	4	0.0–7.4	1.6%	C3	120	2011	4	72.0–94.1	72.8%	B3	2905	2013	1	2.0	2.0%	B0	1593	2009
Indonesia	..	..	..	..	..	..	1	9.7	9.7%	B0	123	2011	2	69.0–83.4	83.4%	B0	145	2010	..	..	..	..	..	..
Malaysia	..	..	..	..	..	..	..	..	..	..	..	..	1	65.8	65.8%	B0	237	2007	..	..	..	..	..	..
Myanmar	1	2.8	2.8%	C2	288	2007	1	3.6	3.6%	B0	8770	2012	1	88.4	88.4%	B2	86	2009	1	3.4	3.4%	C0	1765	2012
Nepal	1	10.8	10.8%	C3	65	2007	1	1.3	1.3%	C3	76	2012	1	96.1	96.1%	B2	120	2010	..	..	..	..	..	..
Thailand	..	..	..	..	..	..	2	3.3–8.4	8.4%	C0	374	2013	1	88.5	88.5%	B2	131	2003	1	1.9	1.9%	C0	275	2013
Vietnam	..	..	..	..	..	..	..	..	..	..	..	..	1	88.5	..	..	..	..	..	..	..	..	..	..
Total‡	10	0–10.7	2.8%	..	..	..	10	1.7–8.4	4.4%	..	..	..	10	71.8–88.4	..	..	..	..	3	1.9–3.4	2.0%	C0	..	..
Eastern Europe and central Asia																								
Estonia	..	..	..	..	..	..	..	..	..	..	..	..	1	56.3	56.3%	C2	80	2004	..	..	..	..	..	..
Kazakhstan	..	..	..	..	..	..	..	..	..	..	..	..	1	82.5	82.5%	B0	183	2012	..	..	..	..	..	..
Latvia	..	..	..	..	..	..	..	..	..	..	..	..	2	85.0–87.5	85.0%	C0	97	2008	..	..	..	..	..	..
Lithuania	..	..	..	..	..	..	..	..	..	..	..	..	1	51.3	51.3%	C2	80	2004	..	..	..	..	..	..
Russia	..	..	..	..	..	..	..	..	..	..	..	..	7	19.0–93.0	60.0%	B3	113	2010	..	..	..	..	..	..
Tajikistan	..	..	..	..	..	..	..	..	..	..	..	..	1	98.3	98.3%	B2	59	2004	..	..	..	..	..	..
Ukraine	..	..	..	..	..	..	..	..	..	..	..	..	2	71.3–97.6	97.6%	C2	82	2004	..	..	..	..	..	..
Total‡	..	..	..	..	..	..	..	..	..	..	..	..	15	56.3–97.6	82.5%	..	..	..	..	..	..	..	..	..

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	General population						Heterosexual or pregnant HIV-infected individual						PWID						MSM					
	Total studies		Best estimate				Total studies		Best estimate				Total studies		Best estimate				Total studies		Best estimate			
	n	Range*	%	Score	n	Year	n	Range*	%	Score†	n	Year	n	Range*	%	Score†	n	Year	n	Range*	%	Score	n	Year
Central Europe																								
Hungary	..	..	..	..	..	..	1	3·9	3·9%	C1	78	2004	..	..	..	..	..	..	..	..	..	..	..	..
Poland	..	..	..	..	..	..	1	29·2	29·2%	B0	120	2011	2	76·6–96·1	76·6%	C2	470	2013	..	..	..	..	..	..
Romania	..	..	..	..	..	..	1	3·7	37%	C1	107	2004	1	40·4	40·4%	C0	193	2012	..	..	..	..	..	..
Slovenia	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1	7·6	7·6%	C3	576	2013
Total‡	..	..	..	..	..	..	3	3·7–29·2	3·9%	..	..	..	3	40·4–76·6	58·5%	..	..	..	1	7·6	7·6%	C3	576	2013
West Europe																								
Belgium	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	4	0·2–15·0	10·0	B0	3081	2009
Denmark	..	..	..	..	..	..	1	7·1	7·1%	B0	4094	2008	1	94·8	94·8%	B0	484	2008	3	4·7–16·2	7·4%	C3	574	2012
France	..	..	..	..	..	..	2	4·0–5·3	4·0%	B0	103	2013	1	83·3	83·3%	C1	66	2004	4	5·0–25·0	5·0%	B0	1959	2005
Germany	..	..	..	..	..	..	..	..	..	..	..	..	2	82·1–92·0	82·1%	C2	84	2004	1	13·3	13·3%	B0	1945	2012
Ireland	..	..	..	..	..	..	..	..	..	..	..	..	1	36·5	36·5%	C2	85	2004	..	..	..	..	..	..
Israel	..	..	..	..	..	..	..	..	..	..	..	..	1	5·2	5·2%	C2	116	2004	..	..	..	..	..	..
Italy	..	..	..	..	..	..	1	11·3	11·3%	B0	1564	2008	7	45·7–96·2	95·2%	B3	84	2008	2	3·0–7·4	3·0%	B0	166	2009
Netherlands	..	..	..	..	..	..	2§	0·4–74·6	0·4%	C0	248	2008	2	91·6–93·9	93·9%	C3	262	2012	11	2·6–17·8	7·1%	B3	439	2012
Norway	..	..	..	..	..	..	..	..	..	..	..	..	1	22·7	22·7%	C2	132	2004	..	..	..	..	..	..
Portugal	..	..	..	..	..	..	1	30·4	30·4%	C2	271	2004	2	36·7–83·8	36·7%	C2	343	2005	..	..	..	..	..	..
Spain	..	..	..	..	..	..	3§	15·2–29·7	23·4%	B3	741	2006	6	69·9–93·8	69·9%	B0	1304	2003	3	0·3–8·8	8·8%	B3	727	2006
Sweden	..	..	..	..	..	..	..	..	..	..	..	..	1	15·1	15·1%	C0	658	2004	..	..	..	..	..	..
Switzerland	..	..	..	..	..	..	1	11·3	11·3%	B3	4530	2011	2	39·4–92·1	92·2%	B3	2678	2011	1	3·2	3·2%	B3	4629	2011
Turkey	..	..	..	..	..	..	3	0·9–12·8	0·9%	B3	949	2013	..	..	..	..	..	..	1	5·0	5·0%	B0	55	2009
UK	..	..	..	..	..	..	2§	1·8–3·0	3·0%	C0	92	2011	3	24·5–82·2	55·3%	B2	76	2007	8	3·5–10·4	5·4%	C0	223	2013
Total‡	..	..	..	..	..	..	16	3–11·3	7·1%	..	..	..	30	36·5–92·1	69·9%	..	..	..	28	5·0–8·8	7·1%	..	..	..
North Africa and Middle East																								
Iran	..	..	..	..	..	..	..	..	..	..	..	..	11	3·9–89·9	88·5%	C3	226	2007	..	..	..	..	..	..
Saudi Arabia	..	..	..	..	..	..	1	3·8	3·8%	C2	234	2010	..	..	..	..	..	..	..	..	..	..	..	..
Sudan	1	5·8	5·8%	B3	96	2013	2	1·7–6·5	1·7%	B3	358	2012	..	..	..	..	..	..	..	..	..	..	..	..
Total‡	1	5·8	5·8%	..	..	..	3	1·7–3·8	2·7%	..	..	..	11	88·5	88·5%	..	..	..	..	..	..	..	..	..

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Region	General population						Heterosexual or pregnant HIV-infected individual						PWID						MSM					
	Total studies		Best estimate				Total studies		Best estimate				Total studies		Best estimate				Total studies		Best estimate			
	n	Range*	%	Score	n	Year	n	Range*	%	Score†	n	Year	n	Range*	%	Score†	n	Year	n	Range*	%	Score	n	Year
East Asia																								
China	:	:	:	:	:	:	4	5·7–21·0	6·9%	B0	662	2011	16	18·4–99·3	96·0%	B2	79	2012	1	1·9	1·9%	C0	513	2012
Taiwan	:	:	:	:	:	:	1	10·9	10·9%	B2	105	2005	10	86·6–98·6	98·6%	B3	297	2010	4	3·6–5·6	3·6%	C3	523	2012
Total‡	:	:	:	:	:	:	5	5·8–14·0	6·9%	:	:	:	26	96·0–98·6	97·3%	:	:	:	5	1·9	1·9%	:	:	:
Asia Pacific and Australasia																								
Australia	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	6	6·5–13·1	6·5%	B3	620	2010
Japan	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	4	2·3–4·2	2·7%	B0	753	2012
South Korea	:	:	:	:	:	:	1	6·5	6·5%	B0	327	2006	:	:	:	:	:	:	:	:	:	:	:	:
Total‡	:	:	:	:	:	:	1	6·5	6·5%	:	:	:	:	:	:	:	:	:	10	2·8–6·4	4·6%	:	:	:
Global total‡	30	0·8–5·8	2·4%	:	:	:	95	1·2–8·4	4·0%	:	:	:	123	55·2–88·5	82·4%	:	:	:	80	3·2–10·0	6·4%	:	:	:

For all population groups see appendix. References for all studies are listed in the appendix. PWID=people who inject drugs. MSM=men who have sex with men. *Range is presented for country level estimates and IQR for regional totals. †Studies were rated and scored according to their study design and assay quality (appendix). Some cells do not have ranges because there is only one study for that country. All best estimates are selected according to the decision rules in the appendix, except for estimates provided for heterosexual people and pregnant women in the Netherlands where the lower assay and study design score was selected to exclude the presentation of an outlier. ‡Totals are derived from median of best estimates scored. Regional totals are IQR. §Denotes estimates (total) derived from samples of HIV-positive pregnant women in the population group of HIV-infected individuals (heterosexual and pregnant women) including Nigeria, 2 (1%, 22%); Malawi, 1 (0·09%); Uganda, 1 (0·6%); Brazil, 2 (5%, 15·5%); USA, 1 (3·8%); Netherlands, 1 (75%); Spain, 1 (29·7%); and UK, 1 (3%).

Table 1: Summary of country and regional HIV-HCV co-infection prevalence estimates in general population samples, Heterosexual or pregnant HIV-infected individuals, PWID, and MSM

Methods

Data extraction and quality assessment

We searched eight databases for studies that reported the prevalence of HCV and HIV, published between Jan 01, 2002, and Jan 28, 2015, following PRISMA guidelines.[24]

Two authors (CM, BM) screened all sources for inclusion, with a third reviewer (LP) consulted when necessary. Data extracted by BM, IY, EG, and LP included study methods, field-work dates, population sampled, recruitment site, sample size, diagnostic assays used, and prevalence of co-infection. For 10% of included studies, data were double extracted by a second author (EG) to check for accuracy.

Studies were rated according to their study design and assay quality (appendix). Studies with larger sample sizes, recruited from several sites, recording age, sex, or HIV risk factors were scored higher, and lower scores were given if no HIV risk factors were reported. HCV antibody assay methods were rated from 0, when no assay type was specified in the study, up to 3, when a second or third generation HCV antibody assay was used with confirmatory testing. Best estimates were selected for each population group per country based on the highest study design and assay score. Where several estimates existed, we applied decision rules to select the best estimate (appendix). We used HCV antibody seropositivity as a measure of overall burden of HCV infection, even though between 20% and 30% of people initially infected and who are HCV-antibody positive will subsequently clear the virus, they will remain antibody positive.

Classification of countries and definition of population groups

Countries were grouped according to the 21 Global Burden of Disease regions, consistent with previous published reviews on HCV burden and further summarised into 12 sub-regions.[3,25]

Populations were classified according to their main HIV exposure categories. General population samples were regarded as low risk, and included samples of blood donors (unpaid), antenatal clinic attendees, or general population surveys, not recruited based on HIV-positive status. Samples of HIV-infected individuals reporting heterosexual transmission as the main risk factor or pregnant women were grouped together. We classified samples as PWID when more than 75% of individuals had experience of injecting drugs, and as men who have sex with men (MSM) when more than 75% of individuals reported their main HIV exposure to be sex with men. These two groups included studies of HIV-infected individuals and populations recruited based on risk behaviour. Other population groups included HIV-infected individuals reporting any injecting drug use (but <75% had experience of injecting), sex workers, prison inmates, drug users (non-injecting), and high-risk populations (recruited from

sexually transmitted infection clinics or a mixed population participating in sexual or drug-injecting risk behaviours, but in which <75% had experience of injecting).

Data analysis

We reported HIV–HCV co-infection prevalence in four population groups by country and region, reporting the best estimate and range for each country. Global and regional prevalence estimates were derived from the median of the best estimates for that region with the IQR. Data were entered into ArcGIS 10.2 to generate maps presenting country-level HIV–HCV co-infection prevalence estimates.

We also synthesised estimates across six independent population groups (general population, PWID, MSM, sex workers, prison inmates, and high-risk populations) on overall HCV co-infection and mono-infection prevalence, and did a meta-analysis across the best estimates of the odds of being HCV-positive in HIV-positive populations compared with HIV-negative populations, stratified by population group. A standard correction of 0·5 was added to all zero prevalence estimates using Stata (version 13.1). Odds ratios were calculated through a Mantel-Haenszel method with a random effects model. Meta-analyses are presented as forest plots.

We report global and regional estimates of burden of HCV co-infection in HIV-infected individuals. Using the number of HIV-infected individuals by country and region estimated by the Joint United Nations

Programmes on HIV/AIDS (UNAIDS),[1] we applied median best estimate of HCV co-infection prevalence in HIV-infected individuals for non-PWID samples from the literature search for MSM, general population, and HIV-positive samples of pregnant women or those heterosexually exposed by sub-regions and then applied the median HCV co-infection prevalence overall. The median best estimate of HCV prevalence in HIV-positive PWID was also applied to the distribution of HIV-positive PWID across subregions, as estimated by UNAIDS.[26] The median of best estimates was applied to generate burden of disease to minimise heterogeneity across the studies. The process of quality assessment used to define best estimates was described earlier (appendix).

Role of the funding source

WHO commissioned this review to inform the update of the WHO guidelines on screening of co-infections and initiation of ART. The funder contributed to the data collection, analysis, interpretation, and writing of the review. All authors had full access to the study data and share final responsibility for the findings submitted for publication.

Results

From 31767 citations, 783 studies met the inclusion criteria resulting in 902 estimates of the prevalence of HIV–HCV co-infection (figure 1).

Co-infection estimates were identified for 88 of the 194 (45%) countries identified in the study (for all

See **Online** for appendix

General population

People living with HIV (heterosexual exposure and pregnant women)

Men who have sex with men

People who inject drugs

Prevalence (anti-HCV)
- No data
- <5%
- 5–15%
- 15–50%
- 50–75%
- >75%
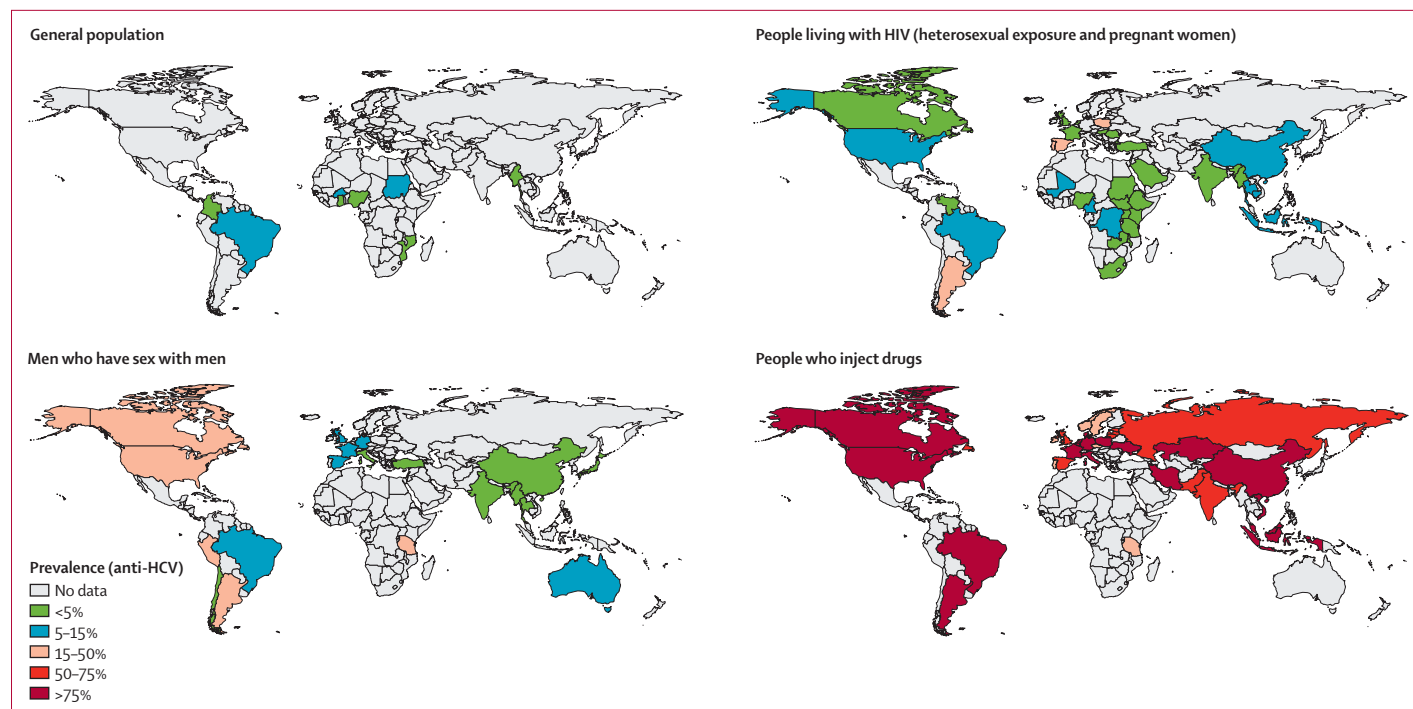
Figure 2: Best estimates of prevalence of hepatitis C virus (HCV) co-infection in four population samples

population groups, not just the groups summarised in table 1). In sub-Saharan Africa, the most estimates were identified in east Africa (11/15 countries), then southern Africa (four of six), and the fewest were in central and west Africa (nine of 24). Seven estimates were identified in north Africa and the Middle East (seven of 21). Estimates were recorded in every country in North America (two of two), but estimates were recorded for only a minority of countries in South America (eight of 21) and the Caribbean (three of 15). Estimates were identified in eight countries in south and southeast Asia (eight of 18), three countries in Asia Pacific and Australasia (three of 17), and one in east Asia (one of two). Nine estimates were identified in eastern European and central Asian countries (nine of 17), 17 in western European countries (17 of 24), and six in central European countries (six of 12).
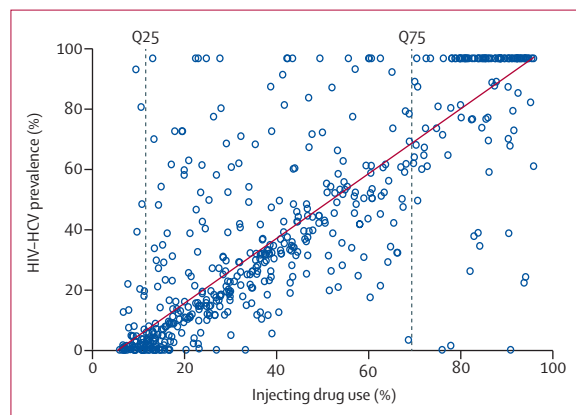
Figure 3: Association between prevalence of injecting drug use and prevalence of HIV–HCV co-infection with interquartile ranges
HCV= hepatitis C virus. Q=quartile.
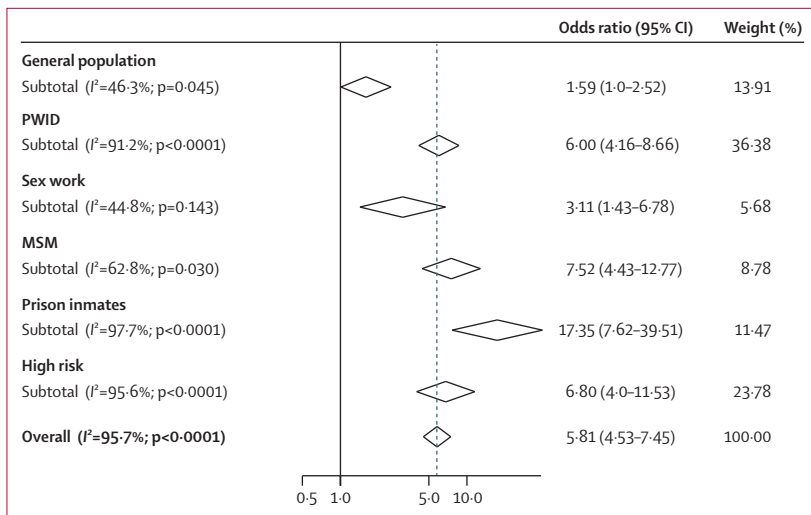
Figure 4: Forest plot showing meta-analysis of odds of HCV antibody in selected HIV-positive populations versus HIV-negative population groups
Weights are from random effects analysis. Full data available in appendix. PWID=people who inject drugs. MSM=men who have sex with men.

The midpoint prevalence of HCV co-infection in 30 HIV-infected general population samples was 2·4% (IQR 0·8–5·8). The highest prevalence was in north Africa and the Middle East and the lowest prevalence was in east Africa (table 1, figure 2). Within these general population samples, prevalence was highest in blood donors at more than 10% in India and Nepal, and 7% in Brazil.[27–30]

The midpoint prevalence of HCV co-infection in 95 studies in HIV-infected individuals (heterosexual people or pregnant women) was 4·0% (IQR 1·2–8·4). Prevalence was highest in west and central Africa and lowest in southern Africa (table 1).

The midpoint prevalence in 80 MSM samples was 6·4% (IQR 3·2–10·0). Prevalence was highest in North America and lowest in east Asia and south and southeast Asia (table 1).

The midpoint prevalence in 123 studies of PWID (≥75% of sample had a history of injecting drug use) was 82·4% (IQR 55·2–84·5) with little regional variation. The highest prevalence was in north Africa and the Middle East and lowest was in western and central Europe. A further 333 estimates were obtained from samples of HIV-infected individuals, for whom injecting drug use was a key exposure, but less than 75% of the sample injected drugs. In these estimates, the median prevalence of injecting drug use was 29·0% (IQR 13·9–46·0). There was a clear association between the prevalence of self-reported injecting drug use and HIV–HCV co-infection prevalence (correlation coefficient 0·89, p<0·001; figure 3).

Across all population groups, there was a 5·8-times (95% CI 4·5–7·5) increased odds of HCV antibody positivity in HIV-positive people compared with HIV-negative people, but with high heterogeneity (I^2 95·7%, p<0·001). Odds of HCV were highest in HIV-positive prison inmates (OR 17·4, 95% CI 7·6–39·5), but similar in MSM (7·5, 4·4–12·7), PWID (6·0, 4·2–8·7), and other high-risk populations (6·8, 4·0–11·5), then lower in sex workers (3·1, 1·4–6·8) and general population samples (1·6, 1·0–2·5). Within-study heterogeneity was high for all population groups except for general population and sex-worker samples for which it was moderate (figure 4).

We estimate that there are 2 278 400 (IQR 1 271 300–4 417 000) cases of HCV co-infection in HIV-infected individuals worldwide, of which 1 362 700 (847 700–1 381 800) are among HIV-positive PWID. This gives a global prevalence of HCV co-infection in HIV-infected individuals of 6·2% (3·4–11·9). Eastern Europe and central Asia has the largest burden, representing 27% of the total burden, which shows the large population of PWID (table 2).

Discussion

To our knowledge, this is the first global systematic review and meta-analysis of the prevalence and burden of HCV in HIV-infected people. We estimate that there are 2·3 million

	HIV-infected individuals (excluding PWID)			HIV-infected PWID				Total HIV-infected individuals* (including PWID)		
	HIV-infected individuals	HCV co-infection		HIV-infected individuals		HCV co-infection		HIV-infected individuals	HCV co-infection	
	n	Median prevalence (IQR)	Estimates (IQR)	n	PWID (%)†	Median prevalence (IQR)	Estimates (IQR)	n	Estimates (range)	Percentage of regional distribution
Africa (south, west, east, central)	25 860 100	1% (1–8)	361 300 (154 800–2 064 500)	92 300	<1%	74% (48–99)	68 300 (44 300–91 400)	25 899 000	429 600 (199 100–2 155 900)	19%
Latin America (South and Central America, Caribbean)	1 688 200	7% (3–16)	116 500 (43 900–270 100)	72 900	4%	82% (24–88)	60 100 (17 600–64 400)	1 761 100	176 600 (61 500–334 500)	8%
North America	1 411 600	12% (6–16)	163 700 (87 500–221 600)	187,000	12%	83% (61–94)	153 300 (114 900–175 100)	1 598 700	319 000 (202 400–396 700)	14%
South and Southeast Asia	2 899 800	3% (2–7)	89 900 (52 200–200 100)	234 600	7%	83% (72–88)	195 700 (168 900–206 400)	3 134 400	285 600 (221 100–406 500)	13%
Eastern Europe and central Asia	832 500	4·8% (2–9)‡	40 000 (16 700–74 900)	688 100	45%	83% (56–98)	567 900 (387 400–671 600)	1 520 600	607 700 (404 100–746 500)	27%
Europe (west, central)	940 200	7% (4–11)	66 800 (34 800–106 200)	53 000	5%	70% (37–91)	37 000 (19 300–48 200)	993 200	103 800 (54 100–154 500)	5%
North Africa and Middle East	185 400	4% (2–6)	7000 (3000–10 800)	52 600	22%	88%	46 500	238 000	53 500 (49 500–57 300)	2%
Western Pacific (Asia Pacific, Australasia)	653 000	6% (3–6)	41 800 (18 300–41 800)	88 300	12%	82% (55–88)	72 700 (48 700–78 100)	741 300	114 500 (67 000–119 900)	2%
East Asia	653 900	4% (2–7)	28 800 (12 400–45 100)	166 100	20%	96%§	159 500§	820 000	188 300 (171 900–204 600)	8%
Total	35 237 400	4·8% (2–9)	915 700 (423 600–3 035 200)	1 635 100	4%	82% (55–88)	1 362 700 (847 700–1 381 800)	36 663 400	2 278 400 (1 271 300–4 417 000)	100%

HCV=hepatitis C virus. PWID=people who inject drugs. *Estimates of HIV-infected individuals in each country were measured through spectrum and published by UNAIDS and UNODC.[1,26] †Proportion of HIV cases in PWID. ‡No regional estimate available, so global median used as a proxy. §No range is reported because there is only one country estimate for PWID in east Asia.

Table 2: Global estimates of HCV infection in HIV-infected individuals by global burden of disease region

(IQR 1·3–4·4 million) cases of HCV co-infection in HIV-infected individuals worldwide, making a global prevalence of 6·2%, of whom 59% are PWID. The greatest burden is in eastern Europe and central Asia, because of the large HIV-infected population of PWID, where an estimated 607 700 HIV-infected people are co-infected with HCV infection, followed by 429 600 in sub-Saharan Africa. Prevalence of HCV co-infection in HIV-infected populations varies widely and is highest in PWID, then MSM, and pregnant or heterosexually exposed populations, and lowest in general population samples.

Our findings corroborate previously published evidence that south Asia, east Asia, and eastern Europe constitute the largest populations of anti-HCV infections.[3,4] We reported clear geographical differences in estimated HIV–HCV co-infection prevalence across population groups. In general population samples, prevalence was highest in South America and west and central Africa and lowest in east Africa. In HIV-positive pregnant women or individuals with heterosexual exposure, prevalence was again highest in west and central Africa, but lower in the rest of sub-Saharan Africa. Previous reviews[16,17] of HIV–HCV co-infection in sub-

Saharan Africa showed a prevalence of between 5·7% and 7% in HIV-positive cohorts, which is within the range of our estimates. One of these reviews also reported similarly high rates of HCV co-infection in west Africa, but far higher rates in southern and east Africa than in our study. An absence of data for risk behaviours made comparison of these regional differences challenging.[17] In PWID, HIV—HCV co-infection prevalence is more than 80% in six regions, particularly in regions where there are large populations of PWID with concentrated HIV epidemics, including central and eastern Europe, south and southeast Asia, and North America.[31]

Our study corroborates other evidence showing the importance of injecting drug use in driving the HCV epidemic in PWID and HIV-infected individuals, and that the highest burden of HCV in PWID is in Russia and China.[25,32] We reported a six-times increase in odds of HCV infection in HIV-positive compared with HIV-negative PWID population groups. This finding is consistent with parenteral transmission being the primary method of HIV and HCV acquisition in PWID, and HCV being much more easily transmitted than HIV.[33] These findings emphasise the urgent need to scale up HIV and

HCV prevention interventions in PWID including needle or syringe exchange programmes, opiate substitution therapy, and provision of ART, both worldwide and especially in eastern Europe and southeast Asia.[34] Additionally, the new era of highly curative short-course direct-acting antiviral therapies for HCV offer the potential to not only improve individual clinical outcomes but also reduce transmission,[35] and therefore emphasises the importance of ensuring equitable access of PWID to HCV testing and direct-acting antiviral treatment.[32,35]

Overall, there was moderate HCV co-infection in HIV-positive MSM samples with an eight-times increase in odds of HCV infection in HIV-infected MSM compared with HIV-uninfected MSM. These data align well with growing evidence suggesting that MSM are increasingly susceptible to HCV transmission, in part fuelled by the use of new psychoactive substances, increased sexual and drug-injecting risk, and sero-sorting within this risk group.[36,37] Evidence also suggests high rates of HCV re-infection after spontaneous clearance or treatment in HIV-positive MSM, emphasising the need for repeated testing and targeted interventions in this population.[38]

Despite a systematic search of published and unpublished scientific literature, estimates were identified in only 45% of countries worldwide, with few country-level estimates in general population samples. The study quality was variable, emphasising the need for more robust surveillance of HCV in HIV-infected individuals, increased transparency in the methods used, and availability of estimates to help monitoring of worldwide trends. The higher co-infection prevalence in blood donors clearly shows the continued need for careful screening of blood donations for HCV and emphasises the difficulties in inferring general population prevalence from this population.[27–30] In view of this potential bias, our general population estimate for co-infection could be an over-estimate, although it falls within the range of previously published, regionally focused reviews, and estimates are consistently lower than for other groups engaging in higher-risk behaviours. Prevalence in blood donors was higher in studies done before 2008 than in more recent studies, indicative of improved screening of donors.[17,28,39–41] The high level of within-study heterogeneity within our meta-analysis urges some caution in our interpretation of the effect of HIV positivity on odds of HCV infection, particularly for prison inmates where the confidence intervals are wide, PWID, and high-risk populations.

Our global study focused on published literature and did not include an exhaustive review of grey literature, as applied in other systematic reviews of this kind,[42] although the inclusion of WHO and Global Health databases captured some unpublished grey literature. We lastly acknowledge that our focus on HCV antibody prevalence fails to fully establish the burden of active HCV infections in HIV-infected individuals (determined by HCV RNA positivity). Only 92 (10%) of our estimates contained data for HCV RNA, most of which (47%) were derived from studies in North America or western Europe. An estimated 20–30% of those exposed to HCV antibodies will spontaneously clear the virus and be HCV RNA negative but remain antibody positive and this might differ across populations.[43,44] In view of the paucity of data and diversity in geographical regions, populations, and risk groups covered in our study we deemed that a focus on antibody prevalence is better for showing the epidemiology of exposure and infection.

International guidelines recommend HCV screening for HIV-infected individuals in many settings, and provision of appropriate HCV care and access to direct-acting antiviral treatment for those with chronic active infection.[19–23] However, this approach is poorly implemented, particularly in low-income and middle-income settings, and in populations such as PWID, prisoners, sex workers, and MSM, where access to care and treatment are already challenging.[32,45] Countries should ensure implementation of existing recommendations for screening of all blood donors and promote routine testing of HCV in all HIV-infected individuals. Targeted and outreach approaches are needed for PWID and MSM because stigmatisation and other factors might limit their access to services for testing and treatment. Improvement of country-level data for prevalence of HCV in all populations is needed to help them to define their epidemiology and inform policies for hepatitis C testing, prevention, care, and treatment. This is particularly important in countries with growing populations of PWID and concentrated HIV epidemics in PWID and MSM, but also in sub-Saharan Africa where the burden of co-infection is large owing to the high burden of HIV. This approach will need investment in building HCV surveillance and care and treatment capacity.

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