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

Lucy Platt PhD[1], Philippa Easterbrook MD[2,] Erin Gower MPH[3], Bethan McDonald PhD[1], Keith Sabin PhD[4], Catherine McGowan PhD[1], Irini Yanny MBChB [1], Homie Razavi PhD[3], Professor Peter Vickerman D.Phil.[5]

1. Faculty of Public Health & Policy, London School of Hygiene & Tropical Medicine, Keppel Street, London, WC1E 7HT, UK
2. Global Hepatitis Programme, HIV Department, World Health Organization, Geneva, Switzerland
3. Centre for Disease Analysis, Boulder, Colorado, USA
4. UNAIDS, Geneva, Switzerland
5. School of Social and Community Medicine, University of Bristol, UK

Please address correspondence to:
Dr. Lucy Platt
Faculty of Public Health & Policy
London School of Hygiene & Tropical Medicine
Tavistock Place
London WC1H 9SH
+44 (0)207 958 8156
Lucy.Platt@lshtm.ac.uk

Abstract

Background:

There are 37 million people living with HIV (PLHIV) and 115 million people with antibodies to Hepatitis C (HCV). Little is known about the extent of HIV/HCV co-infection. We sought to characterise the epidemiology and burden of HCV co-infection among PLHIV.

Methods:

We searched MEDLINE, EMBASE CINAHL+, POPLINE, Africa-wide Information, Global Health, Web of Science, and WHO databases for studies measuring prevalence of HCV and HIV, published from 2002-2015. 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 PLHIV. We conducted a meta-analysis to estimate the odds of HCV among PLHIV compared to their negative counterparts.

Findings:

Among PLHIV, HIV/HCV co-infection is 2·4% (IQR=0·8-5·8%) within general population samples, 4% (IQR 1·2-8·4%) within pregnant or heterosexually exposed samples, 6.4% (IQR 3·2-10·0%) among men who have sex with men (MSM) and 82·4% (IQR 55·2-88·5%) among people who inject drugs (PWID). Odds of HCV infection is 6 times higher among PLHIV. Globally, there are 2·3 million HIV/HCV co-infections (IQR 1·3-4·3) of whom 1.3 million (IQR 0.8-1.4) are PWID, equalling an overall co-infection prevalence among PLHIV of 6·2% (IQR 3·4-11·9%).

Interpretation:

We found a consistently higher HCV prevalence among PLHIV across all risk groups and regions, but especially in PWID. There is a clear mandate to prioritise routine testing of HCV among all PLHIV, but targeted approaches are specifically needed for PWID and MSM. There is a need to improve country level monitoring of prevalence of HCV.

INTRODUCTION

HIV and Hepatitis C (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, 2·3 million were newly infected and 1·6 million died.[1] While HIV transmission has declined since 2001, with improved survival due to the scale-up of anti-retroviral therapies (ART), more people are living with HIV than ever before.[2] It was estimated that in 2005 over 184 million people were HCV antibody positive.[3] More recent data suggest this has declined to 115 million (92-149)[4], with this being attributed to improved screening of blood supply, decreases in injecting risk behaviours and differences in prevalence reported from South East Asia. However, other evidence[5] [6] suggests the disease burden remains high, with 3-4 million new infections and 350,000 deaths occurring annually.[3, 7] HCV treatment has been transformed with the advent of direct acting antivirals (DAAs) which offer high cure rates within 12-24 weeks.[8]

The interaction between HIV and HCV co-infection impacts on 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 among HIV-infected mothers.[9, 10] People living with HIV (PLHIV) 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 may also complicate HIV treatment, with some evidence suggesting an increased risk of drug-related hepatoxicity among those on ART.[12] There remains a lack of consistent data on the impact of HCV co-infection on HIV progression.[13] [9, 12]

As PLHIV 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 suggested 4-5 million PLHIV are infected with HCV[14], but relied on a small number of studies and unclear methodologies, while a second reported prevalence from selected studies only.[15] Other reviews have provided estimates for sub-Saharan Africa only[16] [17] or among people who inject drugs (PWID)[18], but there have been no reviews documenting the global burden of HCV co-infection among PLHIV. Reliable estimates are needed to determine 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 co-infection among PLHIV.

METHODS

Search strategy and selection criteria

We searched eight databases for material that reported the prevalence of HCV and HIV, published between 2002 and 2015, following the PRISMA guidelines.[24] The searches were done in January 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. All language sources were included. Search terms included: 'HIV OR Human immunodeficiency virus' and '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 papers with estimates of HCV co-infection among HIV population samples greater than 50, recruited based on HIV infection status or other behavioural characteristic. We excluded editorials or reviews containing no primary data, samples of HCV or HIV/HCV infected individuals, or

samples relying on self-reported infection status. We excluded samples drawn from populations with other co-morbidities or undergoing interventions that put them at greater risk of co-infection.

Screening and data extraction

Two reviewers (CM, BM) screened all sources for inclusion, with a third reviewer (LP) consulted when necessary. Data extracted 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.

Quality assessment

Studies were rated according to their study design and assay quality (Appendix, Box 1). Studies with larger sample sizes, recruited from multiple sites, recording age, sex or HIV risk-factors were scored higher (A) and lower scores (C) were given if none were reported. HCV antibody assay methods were rated from 0 where no assay type was specified, up to 3 when they used a 2nd or 3rd generation HCV antibody assay with confirmatory testing. Best estimates were selected for each population group per country based on the highest study design and assay score. Where multiple estimates existed, we applied decision rules to select the best estimate (Appendix Box 2).

Classification of countries according to Global Burden of Disease region

Countries were grouped according to the 21 Global Burden of Disease regions, consistent with previous published reviews on HCV burden.[3, 25]

Definition of Population groups

Populations were categorised according to their main HIV exposure categories. General population samples were considered low-risk, and included samples of blood donors (unpaid), ante-natal clinic attendees or general population surveys, not recruited based on HIV positive status. Samples of PLHIV reporting heterosexual transmission as the main risk factor or pregnant women were grouped together. We categorised samples as PWID when >75% of individuals had experience of injecting, and as men who have sex with men (MSM) when >75% reported main HIV exposure to be sex with men. These two groups included studies of PLHIV and populations recruited based on risk behaviour. Other population groups included: PLHIV reporting any injecting drug use (but <75% had experience of injecting); sex workers; prison inmates; drug users (non-injecting); high-risk (recruited from STI clinics or a mixed population engaging in sexual and/or injecting risk behaviours but <75% had experience of injecting).

Data synthesis

We reported HIV/HCV co-infection prevalence among 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 inter-quartile range (IQR). Data were entered into ArcGIS 10·2 (Environmental Systems Research Institute, Redlands, CA.) to generate maps presenting country-level HIV/HCV co-infection prevalence estimates.

We 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 undertook a meta-analysis across the 'best' estimates of the odds of being HCV-positive among HIV-positive populations compared to HIV-negative populations, stratified by population group. A standard correction of 0·5 was added to all zero prevalence estimates using STATA 13·1 (Stata Corp, College Station, Tex). Odds ratios were calculated through a Mantel-Haenszel method with a random-effect model. Meta-analysis are presented as forest plots.

We report global and regional estimates of burden of HCV co-infection among PLHIV. Using number of PLHIV by country and region estimated by the Joint United Nations Programmes on HIV/AIDS (UNAIDS)[1], we applied the median HCV co-infection prevalence among PLHIV 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 overall. The HCV prevalence among HIV-positive PWID was also applied to the distribution of HIV-positive PWID across sub-regions, as estimated by UNAIDS.[26]

Role of the funding source

The 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 a total of 31,767 publication references, 783 papers met the inclusion criteria resulting in 902 estimates of the prevalence of HIV/HCV co-infection (Figure 1).

Availability of estimates by region

Co-infection estimates were identified for 89 of the 194 countries (46%). In Sub Saharan African, the most estimates were identified in East Africa (11/15), then South Africa (4/6), and fewest in Central and West Africa (9/24). A total of seven estimates were identified in North Africa and the Middle East (7/21). Estimates were found in every country in North America (n=2) but the minority of countries in South America (8/21) and the Caribbean (3/15). Estimates were identified in 8 countries in South and South East Asia (8/17), three countries in Asia Pacific and Australasia (n=17), and one in East Asia (n=2). Across Europe, a total of 9 estimates were identified in Eastern European (9/12) and Central Asian countries, 18 in Western (18/24) and 5 in Central European countries (5/12).

Prevalence of HIV/HCV co-infection

General population samples

The mid-point prevalence of HCV co-infection among 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 (5.8%) and the lowest prevalence in East Africa (0.6%). Within these general population samples, prevalence was highest among blood donors at >10% in India and Nepal, and 7% in Brazil.[27-30] All estimates are summarised in Table 1.

PLHIV (heterosexual and pregnant women)

The mid-point prevalence of HCV co-infection among 95 studies in PLHIV (heterosexual /pregnant women) was 4·0% (IQR 1·2-8·4%). Prevalence was highest in West and Central Africa (9·0%, IQR 8·0-11·0) and lowest in Southern Africa (0·5%, IQR 0-1·0%).

MSM

The mid-point prevalence among 80 MSM samples was 6·4% (IQR 3·2-10·0%). Prevalence was highest in North America (16·2%, IQR= 15·2-17·3%) and lowest in East Asia and South and South East Asia (2·0%).

PWID

The mid-point prevalence among 123 studies of PWID (≥75% of sample ever PWID) was 82·4% (IQR 55·2-84·5%) with little regional variation. The highest prevalence was in North Africa/Middle East (88·5%) and lowest in Western and Central Europe (69·9% and 58·5% respectively). There were a further 333 estimates from samples of PLHIV, where injecting drug use was a key exposure but <75% of the sample injected drugs. Among these estimates, the median prevalence of injecting drug use was 29·0% (IQR 13·9-46·%). There was a clear association between the prevalence of self-reported injecting drug use and HIV/HCV co-infection prevalence (Figure 3 – correlation coefficient 0·89, p<0.001).

Odds of HCV infection among HIV-positive relative to HIV-negative persons

Across all population groups, there was a 5·8-fold (95% CI 4·5-7·5) increased odds of HCV positivity among HIV-positive compared to HIV-negative persons, but with high heterogeneity (I squared 95·7%, p<0·001). Odds of HCV were highest among HIV-positive prison inmates (OR=17·4, 95%CI 7·6-39·5), but comparable among MSM (OR=7·5 95% CI 4·4-12·7), PWID (OR=6·0, 95%CI 4·2-8·7) and other high-risk populations (OR=6·8 95%CI 4·0-11·5), then lowest among sex workers (OR=3·1, 95%CI 1·4-6·8) and general population samples (OR=1·6, 95% CI 1·0-2·5). Within study heterogeneity was high for all population groups except for general population and sex-worker samples where it was moderate. See Figure 4 and Online Table 2.

Global burden of HCV co-infection among PLHIV

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

DISCUSSION

This is the first global systematic review of the prevalence and burden of HCV among HIV infected persons. We estimate 2·3 million (IQR 1·3-4·4 million) cases of HCV co-infection among PLHIV globally, making a global prevalence of 6·2%, of whom 59% are PWID. The greatest burden is in Eastern Europe and Central Asia, due to the large HIV-infected population of PWID, where an estimated 607,700 HIV infected persons are co-infected with HCV infection, followed by 429,600 in Sub Saharan Africa. Prevalence of HCV co-infection among HIV-infected populations varies widely and is highest among PWID (82·4%, 55·2-88·5%), then MSM (6·4%, 3·2-10·0%) and pregnant or heterosexually exposed populations (4·0%, 1·2-8·4%), and lowest among general population samples (2·4%, 0·8-5·8%).

Findings corroborate previous evidence that South Asia, East Asia and Eastern Europe constitute the largest populations of anti-HCV infections.[3, 4] We found clear geographic differences in estimated HIV/HCV prevalence across population groups. Among general population samples, prevalence was highest in South America (3·9%) and West and Central Africa (3·6%) and lowest in East Africa (0·6%). Among HIV-positive pregnant women or those with heterosexual exposure, prevalence was again highest in West and Central Africa (9%), but lower in the rest of Sub-Saharan Africa. Previous reviews of HIV/HCV co-infection in Sub-Saharan Africa found a prevalence of between 5·7% and 7% among HIV positive cohorts, which is within the range of our estimates.[16, 17] One of these reviews also reported comparably high rates of HCV co-infection in West Africa, but higher rates in South and East Africa than our review. A lack of data on risk behaviours made comparison of these regional differences challenging.[17] Among PWID, HIV/HCV co-infection prevalence is higher 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 South East Asia and North America.[31]

PWID

This global review corroborates other evidence showing the importance of injecting drug use in driving the HCV epidemic among PWID and PLHIV, and that the highest burden of HCV among PWID is in the Russian Federation and China. [25, 32] We found a six-fold increased odds of HCV infection among HIV positive compared to HIV negative PWID population groups. This is consistent with parenteral transmission being the primary mode of HIV and HCV acquisition among PWID, and HCV being much more easily transmitted than HIV.[33] These findings highlight the urgent need to scale-up HIV and HCV prevention interventions among PWID including needle/syringe exchange programmes, opiate substitution therapy and provision of ART, both globally and specifically in Eastern Europe and South East Asia.[34] In addition, 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 DAA treatment.[32, 35]

MSM

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

Data limitations

Despite a systematic search of published and unpublished literature, estimates were only identified in 46% of countries globally, with few country-level estimates among general population samples. The study quality was variable highlighting the need for more robust monitoring of HCV among PLHIV, and increased transparency in the methodologies used as well as availability of estimates to facilitate monitoring of global trends. The higher co-infection prevalence among blood donors clearly shows the need for careful screening of blood donations for HCV and highlights the problems in inferring general population prevalence from this population. [27-30] Given this potential bias, it is possible that our general population estimate for co-infection is an over-estimate, although it falls within the range published in previous regionally-focussed reviews and estimates are consistently lower than for other groups engaging in higher-risk behaviours. Higher prevalence among blood donors were observed in studies conducted prior to 2008 than more recent studies, indicative of improved screening of donors.[17 28, 39-41] The high level of within-study heterogeneity within our meta-analysis urge some caution in our interpretation of the impact 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 review focussed on published literature and did not include an exhaustive review of grey literature, as applied in other systematic reviews of this kind[42], though the inclusion of WHO databases and Global Health captured some unpublished grey literature. We lastly acknowledge that our focus on HCV antibody prevalence fails to fully determine the burden of active HCV infections

among PLHIV (determined by HCV RNA positivity). Only 10% (92) of our estimates contained data on HCV RNA, the majority of which (47%) were derived from studies in North America or Western Europe. It is estimated that between 20-30% of those exposed to HCV antibodies will spontaneously clear the virus and be HCV RNA negative but remain antibody positive and this may differ across populations.[43, 44] Given the paucity of data and diversity in geographic regions, populations and risk groups covered in the review we considered that a focus on antibody prevalence better reflects the epidemiology of exposure and infection.

Conclusion

International guidelines recommend HCV screening for PLHIV in many settings, and provision of appropriate HCV care for those chronically infected.[19-23] However, this is currently poorly implemented, particularly in low and middle income settings, and among populations such as PWID, prisoners, sex workers and MSM.[32, 45] There is a clear mandate to prioritise screening of blood donors and routine testing of HCV among all PLHIV, but targeted approaches are needed for PWID and MSM where the magnitude of HCV infection risk has not been met with a commensurate investment in surveillance, testing and treatment. There is also a need to improve country-level data on prevalence of HCV among all populations to help them 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 among PWID and MSM, but also in Sub-Saharan Africa where the burden of co-infection is large due to the high burden of HIV. This will need investment in building HCV surveillance and care and treatment capacity.

Research in context

Previous reviews of HIV/HCV co-infection have focussed on specific regions or sub-populations or not employed systematic review methodologies to extract and synthesise data. Data are needed to establish the global burden of HCV co-infection among PLHIV, identify the populations at risk and the key geographical regions most affected. This is essential in order to inform normative guidance and service delivery for testing and care and treatment services.

What this study adds

We estimate a mid-point of 2·3 million (IQR 1·3-4·3 million) cases of HIV/HCV co-infection globally, of whom over half - an estimated 1.3 million (IQR 0·89-1·4 million) are PWID. This equates to a global HCV co-infection prevalence of 6·2% (IQR 3·4-11·9%) among PLHIV. The greatest burden of HIV-HCV co-infection is in Eastern Europe, where an estimated 607,700 HIV infected persons are co-infected with HCV infection, followed by 429,600 in Sub-Saharan Africa. Prevalence of HCV co-infection among PLHIV is highest (82·%, 55·2-88·5%) among PWID, comparable among MSM (6·4%, IQR=3·2-10·0%) and pregnant or heterosexually exposed populations (4·0%, 1·2-8·4%), and lowest among general population samples (2.4%, IQR=0·8-5·8%). Odds of HCV infection is 6 times higher among PLHIV than HIV negative populations ranging from 1.6 times higher among the general population, 3 times higher among sex workers and 6-8 times higher among MSM, PWID and high risk populations.

Implications

Our findings clearly shows that PLHIV are at high risk of HCV infection, particularly PWID who constitute 58% of the global burden of HCV co-infections among PLHIV. Routine testing of HCV among PLHIV is needed, but especially among PWID and MSM including good linkage to care and treatment. There is also a need to improve country level monitoring of prevalence of HCV among all population groups, both HIV positive and negative groups, to define the epidemiology and to inform hepatitis C testing, prevention, care and treatment services. This will require commensurate investment in building HCV surveillance and care and treatment capacity.

AUTHORS AND CONTRIBUTORS

PE conceived the study proposal and LP, PV and PE developed the overall methods for use in the report. LP developed the methodology and oversaw the search and data extraction for the report. CM developed and conducted the literature search. LP, BM, EG and IY extracted data. LP, PE, HR and EG developed the quality assessment tool and LP and EG independently assessed the quality of each record included and selected best estimates. LP and PV developed the analysis technique and LP generated regional and global prevalence estimates, which were reviewed by PE, PV, HR and KS. KS generated the global burden of disease estimates. LP led the writing of the manuscript; PE, PV, HR and BM commented and contributed text. HR generated the maps.

ACKNOWLEDGEMENTS

The authors wish to thank Jane Falconer (Information Services Librarian at the LSHTM) for her assistance with the search strategy and to Katie Ravazi-Shearer for her technical support in producing the maps as well as HIV Regional Advisors in WHO regional offices for assistance with identifying potential unpublished studies from their regions: Massimo Ghidinelli, Laura Alves de Souza (PAHO), Razia Pendse (SEARO), Gabriele Riedner (EMRO), Ying Ru Lo (WPRO), Martin Donoghoe (EURO), Frank Lule (AFRO).

DISCLAIMER

The views and opinions expressed herein are those of the authors and not necessarily UNAIDS OR the WHO.

CONFLICTS OF INTEREST

No conflicts of interest to declare.

Figure 1: Flow chart of included studies

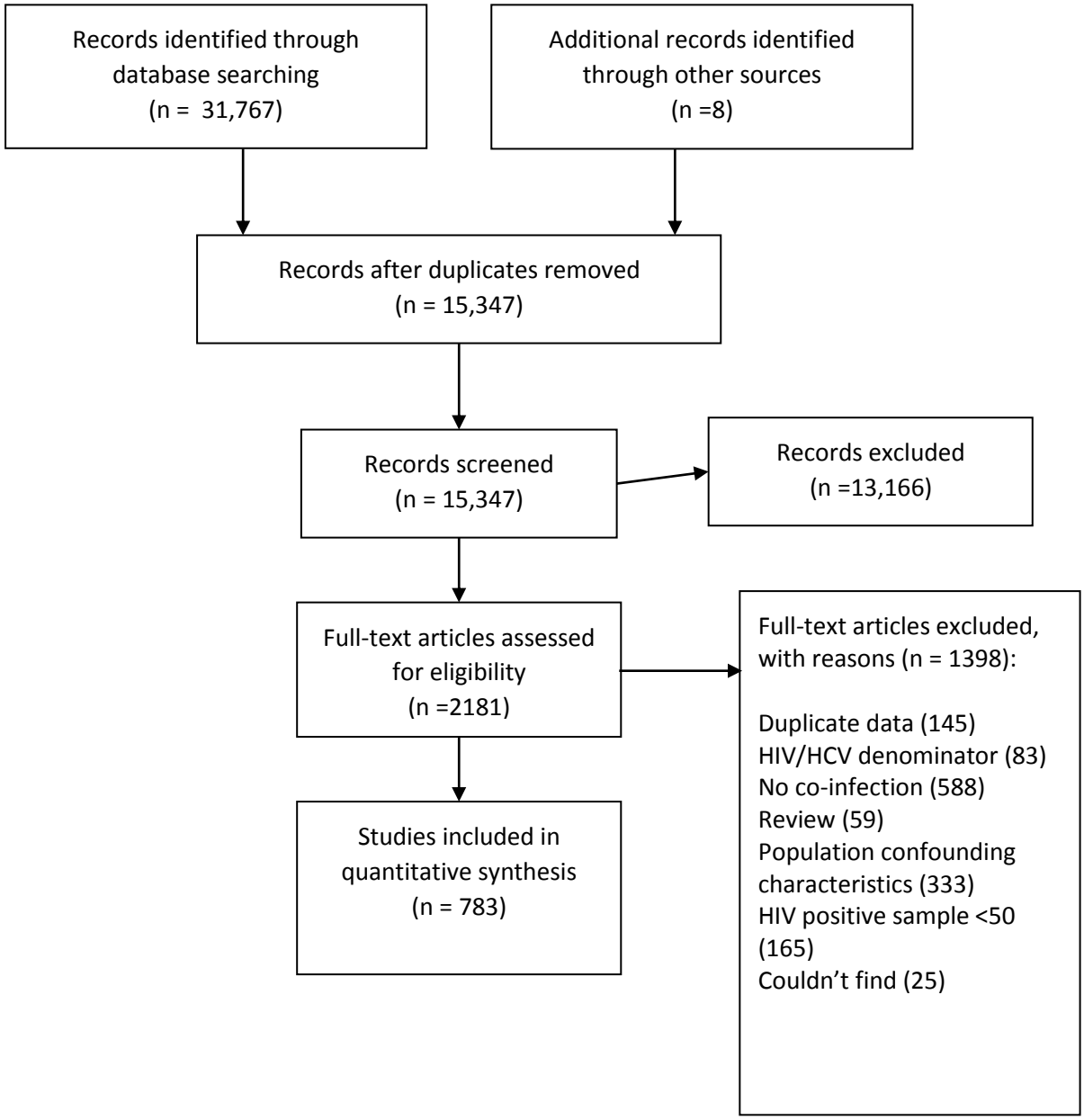

Table 1: Summary of global HIV/HCV co-infection estimates among general population samples, PLHIV, PWID and men who have sex with men

	General Population						Heterosexual /Pregnant PLHIV						PWID						MSM					
	Total studies		Best estimate				Total studies		Best estimate				Total studies		Best estimate				Total studies		Best estimate			
Region/Coun	**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	1	C2	169	2003												
Congo							1	10·0	1	B2	209	2008												
Gambia							1	11·0	1	C0	572	2009												
Ghana	2	0·0-3.6	3.6	B2	168	2012																		
Mali							1	8·0	8·	B2	242	2004												
Nigeria	4	2·0-15·0	2·4	C2	83	2009	13	0·7-22·0	0.	C1	404	2012												
Senegal							1	8·0	8·	C2	363	2002												
Total ǂ	**11**	**2.4-9.6**	**3.6**				**19**	**8-11·0**	**9·**															
SOUTHERN AFRICA																								
Botswana							1	0·0	0·	B2	1995	2006												
Lesotho							1	0·5	0·	B2	205	2007												
South Africa							1	1·0	1·	C2	300	2009												
Total‡							**3**	**0-1·0**	**0·**															
EAST AFRICA																								
Comoros							1	4·0	4·	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.	B2	500	2013												
Kenya							1	1·1	1·	B2	378	2007												
Malawi							3*	0·1-12·7	0·	B3	2041	2011												
Mauritius													1	99·6	99·6	B2	230	2009						
Mozambique	1	1·4	1·4	C3	217	2004																		
Rwanda							1	4·9	4·	C3	89	2004												
Uganda							3*	0.4-3·3	0·	C0	4775	2011												
Tanzania	1	0·0	0·0	C2	60	2005	1	0.6	0.	C0	17539	2011	1	48.3	48.3	B1	93	2011	1	38·5	38·	B0	65	2007
Zambia							1	1·2	1·	C2	323	2008												
Total‡	**6**	**0-1.3**	**0·6**				**19**	**0·5-3.8**	**1.**				**2**	**48.3-99.6**	**73.9**				**1**	**38·5**	**38·**			
SOUTH AMERICA																								
Argentina							1	21·0	2	C0	357	2008	1	88·3	88·3	B2	77	2001	2	0-29·1	29·	B0	85	2009

	General Population						Heterosexual /Pregnant PLHIV						PWID						MSM					
	Total studies		Best estimate				Total studies		Best estimate				Total studies		Best estimate				Total studies		Best estimate			
Region/Coun	**n**	**Range^**	**%**	**Score**	**n**	**Year**	**n**	**Range^**	**%**	**Score**	**n**	**Year**	**n**	**Range^**	**%**	**Score**	**n**	**Year**	**n**	**Range^**	**%**	**Score**	**n**	**Year**
Brazil	1	7·0	7·0	C3	2865	2006	3*	5·6-15·5	8·	C2	63	2010	3	21·0-82·4	82·4	B2	205	2003	1	6	6	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·	C3	162	2003
Venezuela							2	0·7-15·4	0·	C3	418	2008												
Total‡	**2**	**0·8-7·0**	**3·9**				**6**	**0.7-21·0**	**8·**				**4**	**82·4-88.3**	**85·5**				**5**	**4·3-22·5**	**11·**			
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·	C0	94	2009	6	82·4-95·4	82·3	B0	170	2010	3	11·8-26·0	17·	C0	208	2009
USA							8*	3·8-29·4	8·	B0	243	2011	13	8·0-94·7	83·5	B3	158	2012	13	0·6-15·7	15·	B0	92	2011
Total‡							**10**	**4·3-8·0**	**6·**				**19**	**82·5-83·5**	**82·9**				**16**	**15·7-17·3**	**16·**			
SOUTH AND SOUTH EAST ASIA																								
Cambodia							1	5·3	5·	B3	3089	2012												
India	8	0-29·4	0·0	B3	91	2013	4	0·0-7·4	1·	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·	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·	B0	8770	2012	1	88·4	88·4	B2	86	2009	1	3·4	3·4	C0	176	2012
Nepal	1	10·8	10·8	C3	65	2007	1	1·3	1·	C3	76	2012	1	96.1	96.1	B2	120	2010						
Thailand							2	3·3-8.4	8·	C0	374	2013							1	1·9	1·9	C0	275	2013
Vietnam													1	88·5	88·5	B2	131	2003						
Total‡	**10**	**0-10·7**	**2.8**				**10**	**1·7-8·4**	**4·**				**10**	**71·8-88·4**	**83·4**				**3**	**1·9-3·4**	**2·0**			
EASTERN EUROPE & 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**									

	General Population						Heterosexual /Pregnant PLHIV						PWID						MSM					
	Total studies		Best estimate				Total studies		Best estimate				Total studies		Best estimate				Total studies		Best estimate			
Region/Coun	**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·	C1	78	2004												
Poland							1	29·2	2	B0	120	2011	2	76·6-96·1	76·6	C2	470	2013						
Romania							1	3·7	3·	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·**				**3**	**40·4-76·6**	**58·5**				**1**	**7·6**	**7·6**	**C3**		
WEST EUROPE																								
Belgium																			4	0·2-15·0	10·	B0	3081	2009
Denmark							1	7·1	7·	B0	4094	2008	1	94·8	94·8	B0	484	2008	3	4·7-16·2	7·4	C3	574	2012
France							2	4-5·3	4·	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·	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	1	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·	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	3	C2	271	2004	2	36·7-83·8	36·7	C2	343	2005						
Spain							3*	15·2-29·7	2	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	1	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·	B3	949	2013							1	5	5	B0	55	2009
UK							2*	1·8-3·0	3·	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·**				**30**	**36·5-92·1**	**69·9**				**28**	**5·0-8·8**	**7·1**			
NORTH AFRICA AND MIDDLE EAST																								
Iran (Islamic Republic of)													11	3·9-89·9	88·5	C3	226	2007						
Saudi Arabia							1	3·8	3·	C2	234	2010												
Sudan	1	5·8	5·8	B3	96	2013	2	1·7-6·5	1·	B3	358	2012												
Total‡	**1**	**5·8**	**5·8**				**3**	**1·7-3·8**	**2·**				**11**	**88·5**	**88·5**									
EAST ASIA																								
China							4	5·7-21·0	6·	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	1	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·**				**26**	**96-98·6**	**97·3**				**5**	**1·9**	**1·9**			

	General Population						Heterosexual /Pregnant PLHIV						PWID						MSM					
	Total studies		Best estimate				Total studies		Best estimate				Total studies		Best estimate				Total studies		Best estimate			
Region/Coun	**n**	**Range^**	**%**	**Score**	**n**	**Year**	**n**	**Range^**	**%**	**Score**	**n**	**Year**	**n**	**Range^**	**%**	**Score**	**n**	**Year**	**n**	**Range^**	**%**	**Score**	**n**	**Year**
ASIA PACIFIC & 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·	B0	327	2006												
Total‡							**1**	**6·5**	**6·**										**10**	**2·8-6·4**	**4·6**			
Global total‡	**30**	**0·8-5·8**	**2·4**				**95**	**1·2-8·4**	**4·**				**123**	**55·2-88·5**	**82·4**				**80**	**3·2-10·0**	**6·4**			

‡ Totals are derived from median of best estimates scored. **^** Range is presented for country level estimates and interquartile range for regional totals. All best estimate are selected according to the decision rules in Text Box 2, except for estimates provided for Heterosexual/Pregnant women in the Netherlands where the lower assay and study design score was selected to exclude the presentation of an outlier. * Denotes estimates (total) derived from samples of HIV+ pregnant women among the population group PLHIV (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%, the Netherlands (1) 75%; Spain 29·7%, UK (1) 3%. References for all studies are listed in the Web Appendix.

^

Figure 2: Prevalence of HCV co-infection estimates among HIV positive general population samples, PWID, men who have sex with men and PLHIV (exposed via heterosexual transmission or pregnant women)

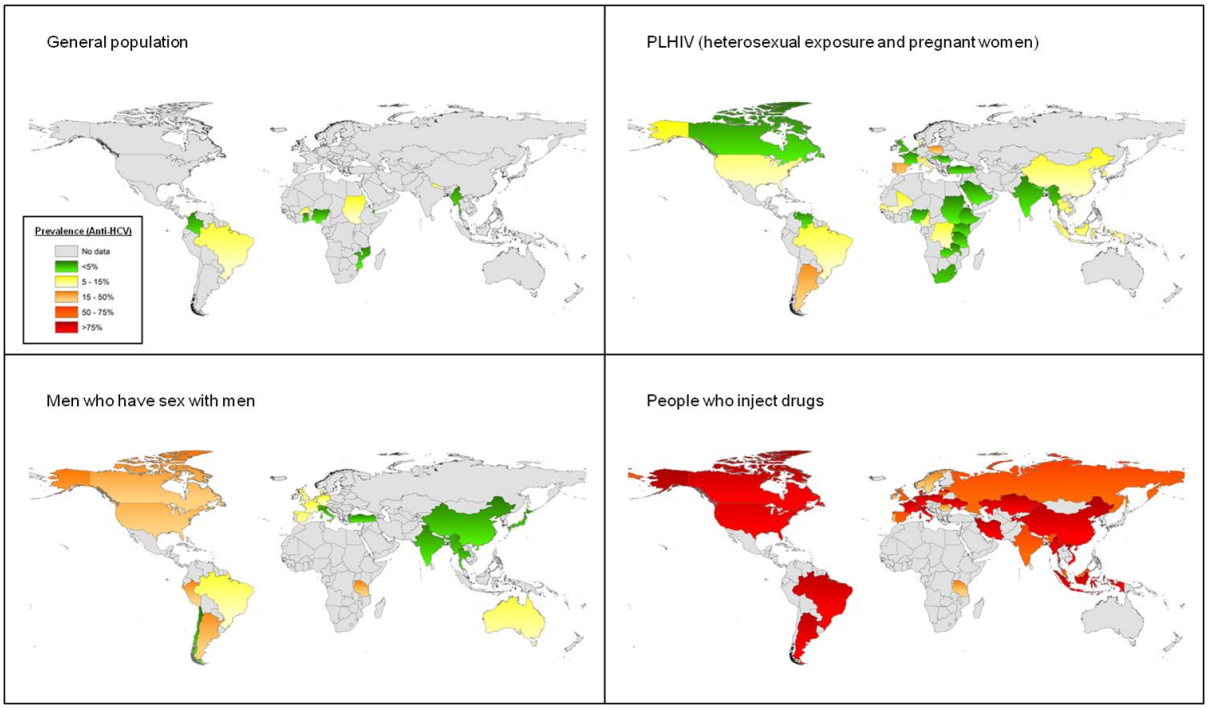

Figure 3: Association between prevalence of injecting drug use and prevalence of HIV/HCV co-infection with interquartile ranges.

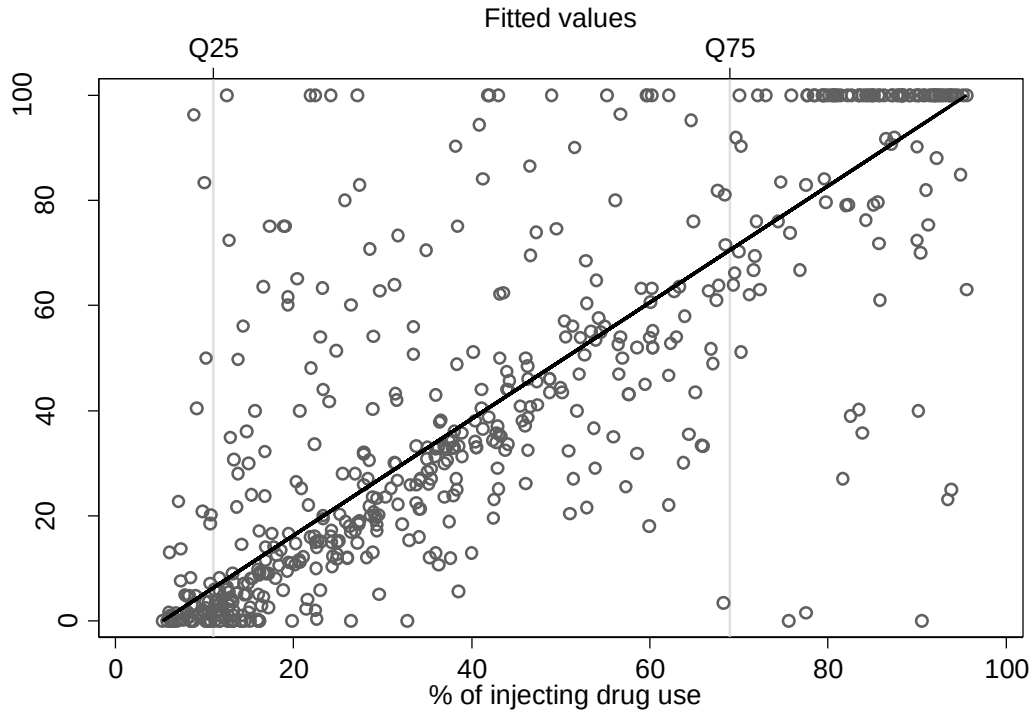

Figure 4: Forest plot showing meta-analysis of odds of HCV antibody positivity among HIV positive populations compared to selected HIV negative population groups

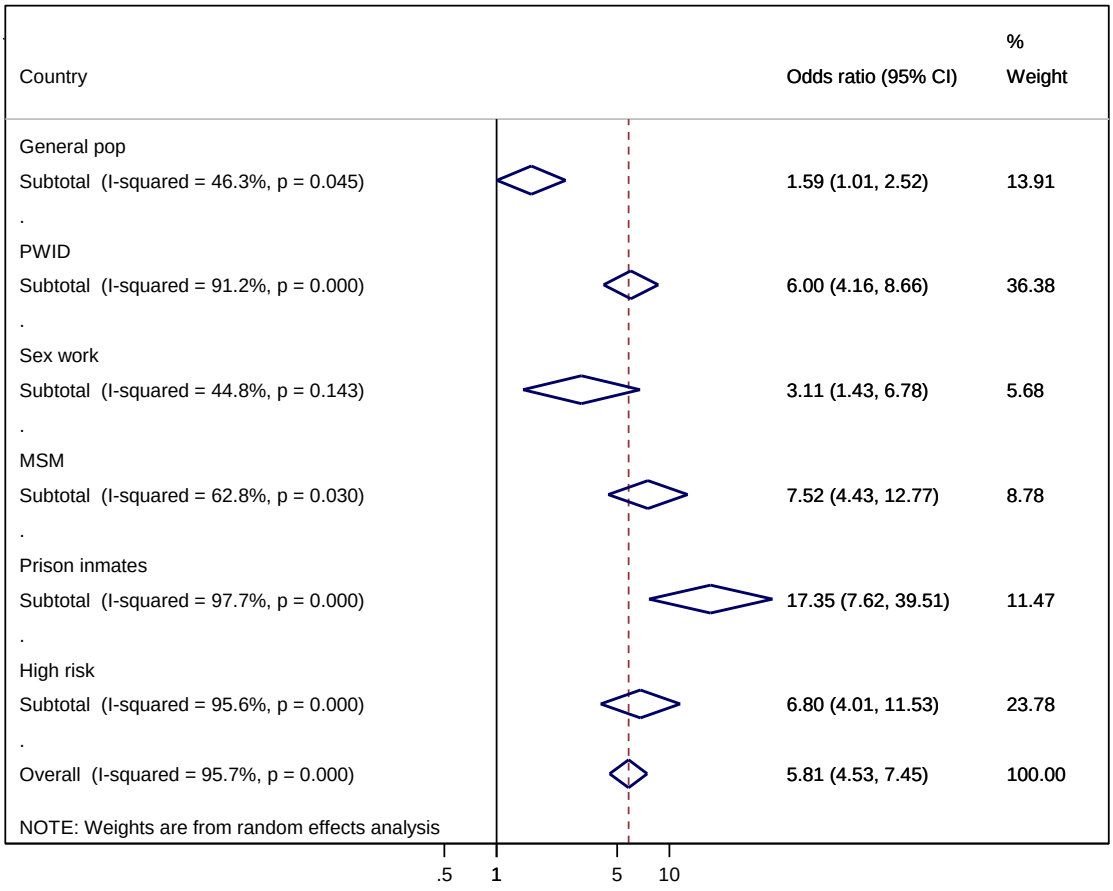

Table 2: Global estimates of HCV infection among People living with HIV by global burden of disease region

Region	PLHIV (excluding PWID)			PLHIV PWID				Total PLHIV*		
	PLHIV	HCV Co-infection		PLHIV		HCV Co-infection		PLHIV	HCV Co-infection	
	n	Median Prevalence (IQR)	Estimates (IQR)	n	% PWID[#]	Median Prevalence (IQR)	Estimates (IQR)	n	Estimates (range)	Regional distribution
Africa (South, West, East, Central)	25,860,100	1% (1-8%)	361,300 (154,800-2,064,500)	92,300	0·4%	74% (48-99%)	68,300 (44,300-91,400	25,899,000	429,600 (199,100-2,155,900)	19%
Latin America (South 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 East 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/ CAR	832,500	4.8% (2-9%)^	40,000 (16,700-74,900)	688,100	45%	83% (56-98%)	567,700 (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%
Eastern Mediterranean	185,400	4% (2-6%)	7,000 (3,000-10,800)	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 (18,300-41800)	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% (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%

*Estimates of persons living with HIV in each country were measured through Spectrum and published by UNAIDS and UNODC[1, 26]

[#]Proportion of HIV cases among PWID ^No regional estimate available, so global median used as a proxy

REFERENCES

1. UNAIDS. How AIDS changes everything. MDG 6: 15 lessons of hope from the AIDS response. UNAIDS, 2015.
2. UNAIDS. Global Statistics. UNAIDS, 2015.
3. Mohd Hanafiah K, et al. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. Hepatology (Baltimore, Md). 2013 Apr;57(4):1333-42
4. Gower E, et al. Global epidemiology and genotype distribution of the hepatitis C virus infection. Journal of hepatology. 2014 Nov;61(1 Suppl):S45-57
5. Hope VD, et al. Prevalence and estimation of hepatitis B and C infections in the WHO European Region: a review of data focusing on the countries outside the European Union and the European Free Trade Association. Epidemiology and infection. 2014 Feb;142(2):270-86
6. Lavanchy D. Evolving epidemiology of hepatitis C virus. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases. 2011 Feb;17(2):107-15
7. Perz JF, et al. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. Journal of hepatology. 2006 Oct;45(4):529-38
8. Doyle JS, et al. Current and emerging antiviral treatments for hepatitis C infection. British Journal of Clinical Pharmacology. 2013;75(4):931-43
9. Sulkowski MS. Viral hepatitis and HIV coinfection. Journal of hepatology. 2008 Feb;48(2):353-67
10. Valle Tovo C, et al. Impact of human immunodeficiency virus infection in patients infected with the hepatitis C virus. Liver International. 2007;27(1):40-6
11. Thomas DL, et al. The natural history of hepatitis c virus infection: Host, viral, and environmental factors. JAMA. 2000;284(4):450-6
12. Shepard CW, et al. Global epidemiology of hepatitis C virus infection. Lancet Infect Dis. 2005 Sep;5(9):558-67
13. 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 Nov 25;356(9244):1800-5
14. Alter MJ. Epidemiology of viral hepatitis and HIV co-infection. Journal of hepatology. 2006;44(1 Suppl):S6-9
15. Peters L, et al. Epidemiology of hepatitis C virus in HIV-infected patients. Curr Opin HIV AIDS. 2015 Sep;10(5):297-302
16. Barth RE, et al. Hepatitis B/C and HIV in sub-Saharan Africa: an association between highly prevalent infectious diseases. A systematic review and meta-analysis. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases. 2010 Dec;14(12):e1024-31
17. Rao VB, et al. Hepatitis C seroprevalence and HIV co-infection in sub-Saharan Africa: a systematic review and meta-analysis. Lancet Infect Dis.
18. Vickerman P, et al. Is the HCV-HIV co-infection prevalence amongst injecting drug users a marker for the level of sexual and injection related HIV transmission? Drug Alcohol Depend. 2013 Sep 1;132(1-2):172-81
19. Soriano V, et al. Care of patients coinfected with HIV and hepatitis C virus: 2007 updated recommendations from the HCV-HIV International Panel. Aids. 2007 May 31;21(9):1073-89
20. Strader DB, et al. Diagnosis, management, and treatment of hepatitis C. Hepatology (Baltimore, Md). 2004;39(4):1147-71
21. Tien PC, et al. Management and treatment of hepatitis C virus infection in HIV-infected adults: recommendations from the Veterans Affairs Hepatitis C Resource Center Program and

National Hepatitis C Program Office. The American journal of gastroenterology. 2005 Oct;100(10):2338-54
22. European Association for the Study of the Liver. EASL Recommendations on Treatment of Hepatitis C 2014.
23. World Health Organisation. Guidelines for screening, treatment and care for persons with hepatitis C. Geneva: World Health Organisation 2014.
24. Liberati A, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration2009 2009-07-21 10:46:49.
25. Nelson PK, et al. Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. Lancet. 2011 Aug 13;378(9791):571-83
26. UNODC. World Drug Report 2014. Vienna: United Nations Office on Drugs and Crime, 2015.
27. Agarwal N, et al. Hepatitis B or Hepatitis C: The bigger threat in multiple infected HIV positive blood donors. Journal of Clinical and Diagnostic Research. 2011;5(4):766-8
28. de Almeida Neto C, et al. Risk factors for human immunodeficiency virus infection among blood donors in Sao Paulo, Brazil, and their relevance to current donor deferral criteria. Transfusion. 2007 Apr;47(4):608-14
29. Karki S, et al. Seroprevalence of HIV and hepatitis C co-infection among blood donors in Kathmandu Valley, Nepal. Southeast Asian J Trop Med Public Health. 2009 Jan;40(1):66-70
30. Myo K, et al. Prevalence and factors associated with hepatitis C virus infection among Myanmar blood donors. Acta Med Okayama. 2010 Oct;64(5):317-21
31. Mathers BM, et al. Global epidemiology of injecting drug use and HIV among people who inject drugs: a systematic review. The Lancet. 2008;372(9651):1733-45
32. Wiessing L, et al. Hepatitis C virus infection epidemiology among people who inject drugs in Europe: a systematic review of data for scaling up treatment and prevention. PLoS One. 2014;9(7):e103345
33. Kiyosawa K, et al. Hepatitis C in Hospital Employees with Needlestick Injuries. Annals of Internal Medicine. 1991;115(5):367-9
34. Mathers BM, et al. HIV prevention, treatment, and care services for people who inject drugs: a systematic review of global, regional, and national coverage. Lancet. 2010 Mar 20;375(9719):1014-28
35. Martin NK, et al. Can antiviral therapy for hepatitis C reduce the prevalence of HCV among injecting drug user populations? A modeling analysis of its prevention utility. Journal of hepatology. 2011 6//;54(6):1137-44
36. van der Helm JJ, et al. The hepatitis C epidemic among HIV-positive MSM: incidence estimates from 1990 to 2007. AIDS. 2011 May 15;25(8):1083-91
37. Wandeler G, et al. Hepatitis C virus infections in the swiss HIV cohort study: A rapidly evolving epidemic. Clinical Infectious Diseases. 2012 November;55(10):1408-16
38. Martin TC, et al. Hepatitis C virus reinfection incidence and treatment outcome among HIV-positive MSM. Aids. 2013 Oct 23;27(16):2551-7
39. Chandra T, et al. Prevalence of transfusion transmitted infections in blood donors: an Indian experience. Trop Doct. 2009 Jul;39(3):152-4
40. Mabayoje VO, et al. Hepatitis C virus co-infection among people living with HIV/AIDS in a Nigerian Teaching Hospital. HIV and AIDS Review. 2013;12(4):102-5
41. Simpore J, et al. HCV and HIV co-infection in pregnant women attending St. Camille Medical Centre in Ouagadougou (Burkina Faso). J Med Virol. 2005 Feb;75(2):209-12
42. Aceijas C, et al. Global estimates of prevalence of HCV infection among injecting drug users. Int J Drug Policy. 2007 Oct;18(5):352-8
43. Kinkel H-T, et al. Prevalence of HIV, Hepatitis B and C Infections and an Assessment of HCV-Genotypes and Two IL28B SNPs among People Who Inject Drugs in Three Regions of Nepal. PLoS ONE. 2015;10(8):e0134455

44. Micallef JM, et al. Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies. J Viral Hepat. 2006 Jan;13(1):34-41
45. Foster GR. Injecting drug users with chronic hepatitis C: should they be offered antiviral therapy? Addiction. 2008;103(9):1412-3