Hepatitis C seroprevalence and HIV co-infection in sub-Saharan Africa: a systematic review and meta-analysis

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Summary

Background An estimated 150 million people worldwide are infected with hepatitis C virus (HCV). HIV co-infection accelerates the progression of HCV and represents a major public health challenge. We aimed to determine the epidemiology of HCV and the prevalence of HIV co-infection in sub-Saharan Africa.

Methods We searched Medline and Embase (Ovid) from Jan 1, 2002, to Dec 31, 2014, for studies containing data for HCV seroprevalence in different population groups in WHO-defined regions of sub-Saharan Africa. We estimated pooled regional prevalence estimates with a DerSimonian-Laird random-effects model. Data were further stratified by risk factor and HIV status.

Findings We included 213 studies from 33 countries in sub-Saharan Africa, comprising 287 separate cohorts with 1 198 167 individuals. The pooled HCV seroprevalence from all cohorts was 2·98% (95% CI 2·86–3·10). The pooled HCV seroprevalence was 2·65% (95% CI 2·53–2·78) across all 185 low-risk cohorts, 3·04% (2·23–3·84) in antenatal clinic groups, 1·99% (1·86–2·12) in blood donors, but 6·9% (6·1–7·5) in other general population cohorts. The pooled seroprevalence of HCV was 11·87% (95% CI 7·05–16·70) across all high-risk groups and 9·95% (6·79–13·11) in patients with liver disease. 101 cohorts included HIV-positive samples tested for HCV (42 648 individuals), with a pooled seroprevalence of 5·73% (95% CI 4·90–6·56).

Interpretation We recorded a high seroprevalence of HCV across populations of sub-Saharan Africa, including in HIV-positive adults, with evidence of regional variation in the general population. Monitoring of antenatal HCV prevalence might be a helpful indicator of population trends in HCV infection; however, larger population surveys are needed to monitor these trends. Access to prevention and treatment needs to be improved for both monoinfected and co-infected individuals.

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Introduction

An estimated 130 million to 150 million individuals worldwide are infected with hepatitis C virus (HCV)[1,2] and the infection contributes substantially to the global burden of disease.[3,4] No vaccine is yet on the market for HCV; therefore, control of the epidemic relies on preventive measures (eg, screening of blood products, opiate substitution, and needle exchange) and on treatment to prevent progression to cirrhosis and hepatocellular carcinoma. Until recently, the complexity of HCV treatment was a barrier to wider use; standard treatment involved injectable pegylated interferon and ribavirin tablets in a long and complex regimen dependent on viral genotype and requiring frequent monitoring.[5,6] HCV management has been revolutionised by recently licensed directly acting antiviral drugs, including protease inhibitors, NS5B inhibitors (eg, sofosbuvir[7,8]), and NS5A inhibitors (eg, ledipasvir and daclatasvir), which allow for shortened treatment durations with improved success rates without the use of interferon.[9,10] These new treatments could substantially reduce the clinical and operational barriers to treatment throughout the world, provided they are accessible and affordable.[6,11]

Accurate epidemiological information is essential to inform treatment and control priorities at national and regional levels. In particular, data are needed on the burden of co-infection with HIV in view of the poor outcomes for HCV in this population.[12] Such data are scarce for many regions, particularly parts of sub-Saharan Africa, partly because the public health importance of HCV infection has only recently been recognised.[3] A 2002 review[13] of HCV epidemiology in sub-Saharan Africa estimated the overall prevalence of HCV to be 3%, with substantial regional variation. A further review[14] of the association between HIV and hepatitis B and C showed a relative risk of HIV co-infection of 1·60 (95% CI 1·05–2·45). However, both analyses identified few data for the prevalence of HIV–HCV co-infection, which is crucial to the policy debate surrounding expansion of HCV treatment.

We did this systematic review and meta-analysis to determine the seroprevalence of HCV and the prevalence of HCV–HIV co-infection across sub-Saharan Africa.

Methods

Search strategy and selection criteria

We searched Medline and Embase (Ovid) from Jan 1, 2002, to Dec 31, 2014, for all reports that possibly contained data for HCV seroprevalence in different population groups. The appendix provides full details of the search strategy and includes terms to assess the availability of data on

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See **Online** for appendix

HIV–HCV co-infection. Included reports were published between Jan 1, 2002, and Dec 31, 2014.[13] One author (NJ) extracted data and another author (VBR) verified these data in full on the basis of country, year of publication, year of collection, study type, study design, HCV assay used, study population, sample size, proportion of men, age, HCV seroprevalence, PCR prevalence, genotype (including proportion of each genotype when available), subtypes, and prevalence of HIV co-infection.

Countries included in the study were limited to those in sub-Saharan Africa, grouped according to WHO Africa regions. To directly compare results with previous published analyses, we excluded six countries: Algeria, Cape Verde, Comoros, Mauritius, São Tomé and Príncipe, and Seychelles. We included three countries not listed in the WHO regional list: Sudan, and South Sudan after 2012], Djibouti, and Somalia. We included studies published in English and French. Studies were not rejected on the basis of sample size or design (including both retrospective and prospective studies), and included cross-sectional national surveys and surveys from screening programmes, antenatal clinics, blood donations, hospitals, and other institutions such as prisons. We excluded studies that did not state sample size or HCV seroprevalence or identify the HCV diagnostic assays used. No study was discounted on the basis of HCV

diagnostic assay; this review includes studies using both non-confirmatory (ELISA, EIA, screening assays) and confirmatory (RIBA, western blots, PCR) assays. The prevalence of detectable HCV RNA was included when available.

Cohort classification

We separated cohorts either by time of collection (if this was defined in the study) or by collection site—ie, antenatal clinic or blood donor. We also separated control cohorts from intervention cohorts in case-control studies. If a study included a separate HIV subanalysis, we included this cohort as separate within the HIV pooled prevalence, but did not count it overall as a separate cohort. We initially categorised cohort studies as either low risk or high risk with definitions similar to those used previously.[13] The low-risk category followed the definition from Madhava and colleagues[13]—namely, according to the setting from which the samples were obtained and tested. The aggregated low-risk group included pregnant women at antenatal clinics, blood donors, and other samples that were obtained from the general population—ie, randomly selected communities whether rural or urban, students, and samples from inpatients or outpatients seeking care for non-hepatic illnesses or who had not had multiple blood transfusions. We divided the high-risk group into two groups: patients with known liver disease, whether acute or chronic; and patients who had no documented liver disease but who had high-risk exposures such as multiple blood transfusions, haemodialysis, renal transplants, sickle-cell disease, or injecting drug use. We grouped HIV-infected cohorts separately to assess the prevalence of HIV and HCV co-infection.

Statistical analysis

We calculated point estimates and 95% CIs for the proportion of people with HCV in each study. We estimated prevalence of HCV by WHO region by pooling of data from each study. Data were pooled with a DerSimonian-Laird random-effects model,[15] which incorporates an estimate of between-study variance, allowing that the true effect size could vary between studies.[16] To assess between-study heterogeneity for the estimates of pooled prevalence by region, the t^2 statistic was calculated. The variance of raw proportions was stabilised with a Freeman-Tukey type arcsine square-root transformation.[17] Several methods of pooling of proportions exist; the Freeman-Tukey method works well with both fixed-effects and random-effects meta-analysis.[18,19] We further stratified data by risk group and HIV status. We did analyses with Stata (version 12).

Role of the funding source
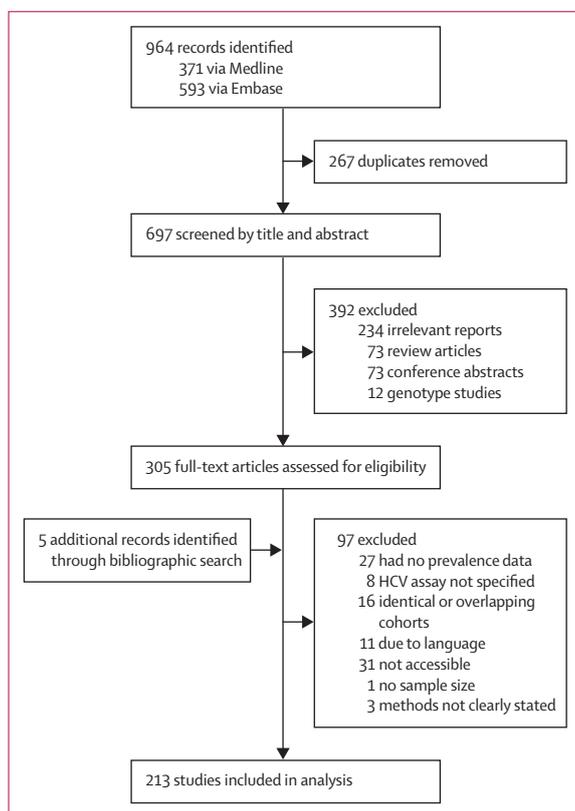
Figure 1: Study selection
HCV=hepatitis C virus.

Flowchart content:

964 records identified
371 via Medline
593 via Embase

267 duplicates removed

697 screened by title and abstract

392 excluded
234 irrelevant reports
73 review articles
73 conference abstracts
12 genotype studies

305 full-text articles assessed for eligibility

5 additional records identified through bibliographic search

97 excluded
27 had no prevalence data
8 HCV assay not specified
16 identical or overlapping cohorts
11 due to language
31 not accessible
1 no sample size
3 methods not clearly stated

213 studies included in analysis

Results

We included 213 studies from 33 countries in sub-Saharan Africa (figure 1, appendix). These studies included data for 287 cohorts comprising 1 198 167 individuals; 241 cohorts had sample sizes greater than 100 people (appendix). 177 studies were cross-sectional surveys, 15 studies were retrospective cohort studies, and 19 studies were case-control studies. Of the 287 cohorts, 81 (28%) used confirmatory assays to screen for the presence of anti-HCV antibodies and HCV RNA, 55 (19%) described testing for HCV RNA (ie, reported HCV prevalence based on PCR testing), and 39 (14%) presented data for HCV genotyping.

The estimated pooled HCV seroprevalence across all 287 cohorts identified was 2·98% (95% CI 2·86–3·10; t² 0·06), varying widely from 6·76% (95% CI 5·98–7·55; t² 0·05; 70 cohorts) in the central Africa region to 4·34% (3·99–4·70; t² 0·05; 142 cohorts) in west Africa and 0·91% (0·80–1·02; t² 0·02; 75 cohorts) in southeast Africa. 142 cohorts (49%) were from the west Africa region, but most individuals were from southeast Africa, skewed by one survey from the South African Blood Service (732 250 samples).[20] 185 cohorts comprising 1 151 337 individuals were identified as low-risk populations (appendix) representing 30 of the 33 countries. The pooled HCV seroprevalence in all low-risk groups aggregated, across all regions of sub-Saharan Africa, was 2·65% (figure 2). This seroprevalence was higher than that in all blood donor cohorts, but lower than that in other general population cohorts (figure 2).

We noted substantial regional variation among the low-risk cohorts (figure 1), with pooled HCV seroprevalence highest in the central Africa region and lowest in southeast Africa (figure 2). West Africa contributed the largest number of cohorts (n=100) and has a seroprevalence that most closely approaches the overall estimate (figure 2). The pooled prevalence was slightly higher in aggregated low-risk populations than in blood donors, but this difference was greatest in the central Africa region (figure 2). The highest HCV seroprevalence estimate in a blood donor cohort included in this analysis was 14·58% from a study that sampled blood donated at teaching hospitals and privately owned blood banks in Nigeria (n=624).[21]

Among antenatal clinic populations, overall pooled HCV seroprevalence was 3·04%, similar to the aggregated pooled estimate for low-risk cohorts (figure 2). However, findings from regional subanalysis, despite low cohort numbers, showed that the pooled HCV seroprevalence for antenatal clinical cohorts in central Africa was again substantially lower than the overall central region estimate in low-risk populations (figure 2). Pooled seroprevalence for antenatal clinic cohorts in the west Africa region was higher than that in the southeast region (figure 2).

A subanalysis of the other 88 cohorts included in the low-risk category—namely, samples from the general population in addition to inpatients and outpatients not deemed to be at a high risk of HCV—showed an overall pooled seroprevalence that was higher than the estimates

for antenatal clinic and blood donor populations (figure 2). Regional variation was substantial, with a pooled seroprevalence estimate in central Africa of 12·11% compared with 2·44% in southeast Africa and 5·74% in west Africa (figure 2). In all regions, pooled estimates in these so-called other low-risk cohorts were higher than those in in antenatal clinic and blood donor populations (figure 2).

41 cohorts across 15 countries were categorised as high risk for HCV infection (figure 3, appendix). Pooled HCV seroprevalence estimates across all 21 high-risk exposure

	Number of studies		Prevalence (95% CI)
Low risk (overall)			
Overall	185		2·65 (2·53–2·78)
Central	50		6·89 (6·00–7·78)
Southeast	35		0·67 (0·57–0·78)
West	100		3·72 (3·38–4·07)
Blood donors			
Overall	76		1·99 (1·86–2·12)
Central	19		2·61 (1·68–3·56)
Southeast	12		0·43 (0·33–0·54)
West	45		3·18 (2·76–3·60)
Antenatal care			
Overall	21		3·04 (2·23–3·84)
Central	5		1·72 (1·25–2·18)
Southeast	2		0·36 (0·00–0·80)
West	14		4·29 (2·95–5·63)
Other low risk*			
Overall	88		6·90 (6·14–7·66)
Central	26		12·11 (9·40–14·82)
South-east	21		2·44 (1·80–3·10)
West	41		5·74 (4·69–6·80)

Figure 2: **Estimated pooled seroprevalence of hepatitis C virus in low-risk populations**
*Other cohorts included the general population, inpatients, and outpatients.

	Number of studies		Prevalence (95% CI)
High risk			
Overall	21		11·87 (7·05–16·70)
Central	6		8·42 (5·09–11·75)
Southeast	6		12·62 (5·96–19·29)
West	9		10·70 (6·19–15·20)
Liver disease			
Overall	20		9·95 (6·79–13·11)
Central	4		2·51 (0·97–4·04)
Southeast	5		11·73 (5·62–17·84)
West	11		13·42 (7·09–19·74)
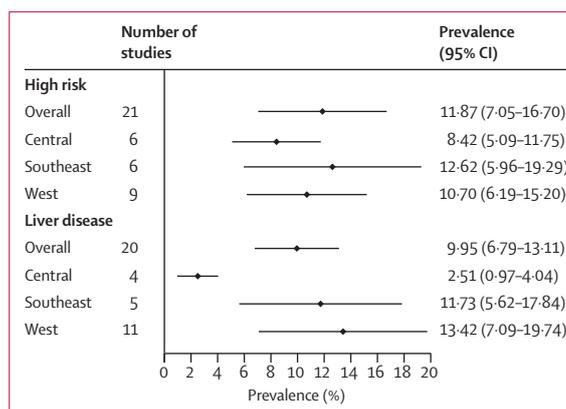
Figure 3: **Forest plot of estimated pooled seroprevalence of hepatitis C virus in high-risk populations**
High-risk populations included individuals who had undergone multiple transfusions, injecting drug users, those who had undergone haemodialysis, health-care workers, and prisoners.

cohorts were higher than those for low-risk cohorts, with similar values across all regions (figures 2, 3). The estimate for high-risk cohorts in the central Africa region was lower than that for the so-called other low-risk cohorts in the same region, although cohort numbers are low (figures 2, 3). The highest HCV seroprevalence estimate identified
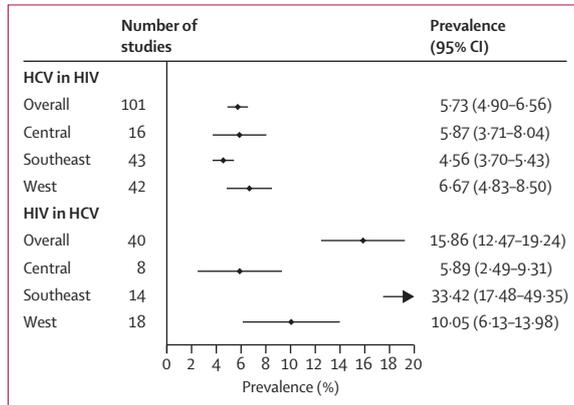
Figure 4: Seroprevalence of HCV in HIV-positive cohorts and of HIV in HCV-positive cohorts, by region
HCV=hepatitis C virus.

Figure 5: Estimated HCV seroprevalence in HIV-positive cohorts in relation to HIV prevalence in 15–49 year olds
HIV data are from WHO/UNAIDS, 2013.[23] HCV=hepatitis C virus.

was recorded in Kenya in a sample population of 145 injecting drug users (46% with HCV).[22] By contrast, analysis of the 20 liver disease cohorts showed an overall pooled HCV seroprevalence estimate of 9·95% (figure 3, appendix). Although estimated levels of infection were similar in west and southeast Africa, in the central region the pooled seroprevalence of HCV in liver disease cohorts was 2·5% (figure 3). This estimate was lower than estimates in this region for the aggregated low-risk cohorts and accorded with estimates for blood donor and antenatal clinic populations in the central region (figures 2, 3).

Seroprevalence of HCV–HIV co-infection was reported in 101 cohorts from 27 countries; some cohorts were recruited as HIV-positive cohorts (n=61) and others were identified as a subgroup within the primary analysis of each study. 42 648 HIV-positive individuals were included (appendix). 75 cohorts (74%) included more than 50 individuals. The overall pooled seroprevalence of HCV co-infection in HIV-infected individuals was 5·73% (figure 4). Most co-prevalence studies were from countries in west Africa, with a pooled HCV seroprevalence of 6·67%, and southeast Africa, with a pooled HCV seroprevalence of 4·56% (figure 4). Estimates of co-infection in HIV-positive cohorts in all regions lie between those for blood donor and antenatal clinic cohorts and high-risk cohorts (figure 4).

Some countries (eg, Senegal, Rwanda, Djibouti, and The Gambia) report fairly low HIV prevalence and low levels of co-infection (figure 5). Some regions of high HIV prevalence (eg, Malawi, Zimbabwe, and Zambia in southern Africa) are estimated to have low levels of HCV co-prevalence (figure 5). We noted the highest levels of co-prevalence in east and southeast Africa (Tanzania, Mozambique, and Kenya) and central Africa (Cameroon, Burundi, and Angola) of which only Mozambique reports HIV prevalence greater than 10% (figure 5). When we considered only countries with either a sample size greater than 500 HIV-positive patients or with more than four HIV-positive cohorts, co-infection with HCV was estimated to be greater than pooled seroprevalence of 10% in Burundi, Cameroon, Kenya, Mozambique, Tanzania, and Burkina Faso, and less than 5% in Uganda, Malawi, South Africa, and Côte d'Ivoire.

We included 40 cohorts with 3422 HCV-infected individuals, with a pooled HIV prevalence of 15·86% (95% CI 12·47–19·24). Regional breakdown showed that the highest rates of HIV co-infection in individuals with known HCV were in southeast Africa (33·42%, 95% CI 17·50–49·35; 14 cohorts) by contrast with west Africa (10·05%, 6·13–13·98; 18 cohorts) and central Africa (5·89%, 2·49–9·31; eight cohorts). In only 52 (28%) of 185 low-risk cohorts confirmatory assays were used to screen for the presence of anti-HCV antibodies. The estimates for pooled HCV seroprevalence overall and in each of the regions did not differ greatly from those in all general population cohorts when restricted to studies using confirmatory assays.
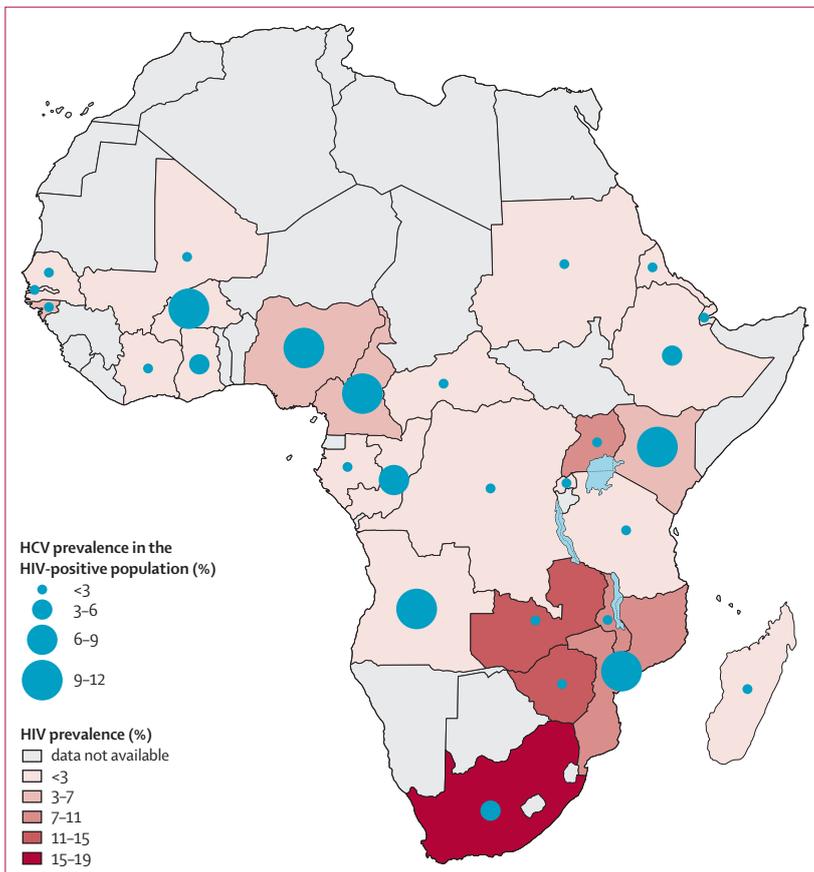
Analysis of the 35 low-risk cohorts that also reported PCR testing showed that the pooled proportion of positive serology samples that were PCR positive was 51·27% (figure 6). Data for the genotype distribution of HCV were reported for only 39 cohorts in 19 countries.

Discussion

We recorded a high seroprevalence of HCV across populations of sub-Saharan Africa, including in HIV-positive adults, when all samples were analysed collectively, with similar, slightly lower, levels of infection when analysis was limited to low-risk samples, in accordance with previous definitions. We identified regional variation among groups considered low risk, with the highest pooled seroprevalence within the central Africa region. In all regions, estimates of HCV seroprevalence were lower in blood donor cohorts and antenatal clinic groups than within aggregated low-risk cohorts. However, the regional and overall pooled seroprevalences in the so-called other low-risk groups were higher. These cohorts included individuals in health-care settings as part of case-control studies or convenience sampling. Such settings are associated with transmission of HCV due to potential nosocomial transmission through fomites or non-exposure prone procedures including venepuncture and cannulation,[14,24–26] and might explain why recorded prevalence was higher than in population surveys.

The overall estimates for HCV seroprevalence are very similar to those described previously, despite the estimates being based on different studies and different time periods.[13] This similarity gives more certainty to the robustness of these estimates and suggests no major change in HCV prevalence between the periods of study. However, larger population surveys, repeated over time, are needed to monitor these trends. Because population surveys are time consuming and expensive, other complementary methods are needed to monitor changes in prevalence. The finding that HCV prevalence in antenatal cohorts is similar to that in the overall population suggests that antenatal groups might represent a useful population for monitoring, particularly because there are many existing programmes testing for HIV in this group.

Previous analyses done as the HIV epidemic arose in sub-Saharan Africa showed little evidence of association between the prevalence of HIV and HCV infections.[13] An increased relative risk of hepatitis B virus and HCV infection has been reported in HIV-positive populations compared with HIV-negative populations.[14] We noted that the overall seroprevalence of HCV infection in HIV-infected individuals was substantially higher than that in blood donor or antenatal clinic groups, and similar to that in general population cohorts, a finding that was consistent across all regions. The highest estimates of HCV–HIV co-infection were in countries (Tanzania, Burkina Faso, Cameroon, and Kenya) with a moderate prevalence of

	Year		Proportion (95% CI)
West Africa			
Ampofo	2002		28·26 (18·33–39·39)
Candotti	2003		47·66 (35·61–59·84)
Rouet	2004		70·50 (28·07–98·16)
Simpore	2006		28·83 (13·39–47·36)
Plamondon	2007		92·68 (85·75–97·44)
Zeba	2011		94·72 (61·43–95·80)
Konidena	2011		50·00 (3·74–96·26)
Konidena	2011		93·30 (53·36–94·88)
Forbi	2012		75·32 (65·28–84·14)
Zeba	2014		33·16 (24·23–42·75)
Ceriani	2014		29·52 (12·77–49·79)
Campo	2014		7·69 (0·31–23·47)
Subtotal			54·04 (34·25–73·82)
Central Africa			
Njouom	2003		68·31 (57·09–78·54)
Njouom	2003		74·16 (56·99–88·16)
Njouom	2005		76·11 (66·81–84·30)
Pasquier	2005		74·88 (68·79–80·51)
Biggar	2006		8·71 (3·07–16·86)
Mudawi	2007		2·57 (2·20–20·57)
Ndong-Atome	2008		90·31 (82·15–96·18)
Ndong-Atome	2008		64·30 (43·14–82·89)
Ndong-Atome	2009		39·26 (16·27–65·12)
Canataloube	2010		61·77 (48·16–74·50)
Seremba	2010		29·59 (17·77–43·00)
Pépin	2010		92·69 (89·17–95·56)
Pépin	2010		81·77 (73·47–88·81)
Foupouapouognigni	2011		9·18 (6·51–58·77)
O'Reilly	2011		18·33 (0·92–50·36)
Njouom	2012		46·37 (41·80–50·96)
Tagny	2014		38·15 (23·56–53·93)
Subtotal			52·22 (36·92–67·53)
Southeast Africa			
Fang	2003		9·18 (6·51–58·77)
Puato	2007		13·28 (6·75–21·60)
Ramarokoto	2008		67·32 (48·47–83·65)
Muasya	2008		68·92 (34·99–94·12)
Reddy	2009		76·26 (62·03–87·99)
Abreha	2011		25·69 (16·33–36·34)
Subtotal			43·05 (18·69–67·42)
Overall			**51·27 (40·32–62·23)**

Proportion (%)

Figure 6: **Proportion of positive serology samples that were PCR positive in 35 low-risk cohorts**
See appendix for full details of the included studies.

adult HIV (<6%, except Mozambique). By contrast, countries with the highest HIV prevalence (South Africa, Botswana, Zimbabwe, Zambia, Mozambique, and Malawi) were all estimated to have low to moderate levels of HCV co-infection (<5%, except Mozambique). Conversely, seroprevalence of HIV co-infection was increased in cohorts identified as HCV seropositive, except in the central Africa region, although our analysis included fewer cohorts and samples from the central Africa region than from southeast or west Africa. These differences suggest that risk behaviours responsible for HCV transmission might be quite dissociated from those associated with HIV transmission in some regions, such as central Africa. Furthermore, regional differences might be partly explained by risk behaviours that are specific to one area (eg, scarification or specific medical practices), but we did not identify large studies that were able to explore this hypothesis further.

Although our meta-analysis of HIV–HCV co-infection is the largest so far, it is limited by the geographical distribution of the reports identified through the systematic review. Although most the reported studies were from the west Africa region, most samples were from southeast Africa, especially South Africa (including one large population survey). Nonetheless, the data here support the need for provision of HCV testing and care in all HIV programmes and developing programmes for HCV infection. Despite retrieval of a large number of studies, we limited our review to published articles retrieved from searching two databases and published in two languages; an expanded search including grey literature and additional languages (notably Arabic and Portuguese) might have contributed additional studies.

The quality of studies included was variable because most were not cross-sectional population-based surveys, but instead targeted specific groups in restricted geographical regions. All the studies assessed HCV infection with serology, a proportion then undertook confirmatory testing. The results of the PCR testing suggest the proportion of seropositive patients who have active disease, and hence need treatment, is just over 50%. The extent to which this finding is a result of false-positive serology, a well recognised challenge, is hard to quantify. However, a subanalysis restricted to those general population samples with confirmed serology showed a prevalence similar to that in all general population samples, suggesting that this issue was not major. Importantly, a large proportion of seropositive individuals will not need treatment and these data reinforce the need for larger community surveys with high-quality diagnostic methods, including HIV and HCV nucleic acid testing, for more robust prevalence estimates to inform development of prevention and treatment programmes. Irrespective of the limitations of the available data, there is a clear unmet need for prevention and treatment, access to which needs to be improved for both monoinfected and co-infected individuals.

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