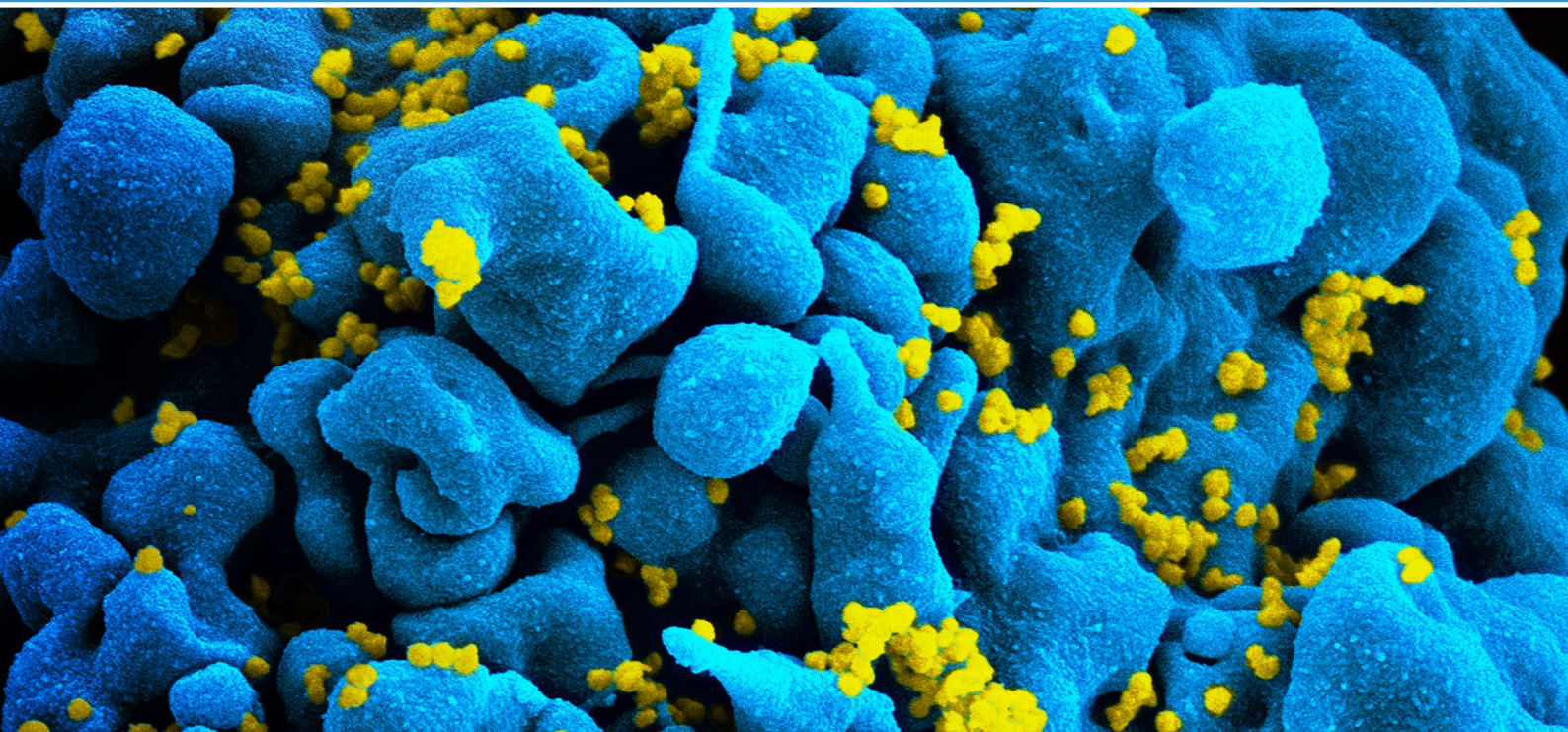




Impact of antiretroviral therapy on liver disease progression and mortality in patients co-infected with HIV and hepatitis C

Systematic review and meta-analysis



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EPPI-Centre report no. 2304
October 2015

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This report should be cited as:

Llewellyn A, Simmonds M, Brunton G, Sowden A (2015) Impact of antiretroviral therapy on liver disease progression and mortality in patients co-infected with HIV and hepatitis C: Systematic review and meta-analysis. EPPI-Centre, Social Science Research Unit, UCL Institute of Education, University College London.
ISBN: 978-1-907345-80-7

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Abbreviations

AIDS	Acquired immune deficiency syndrome
ARV	Antiretroviral
CCR5	Chemokine receptor
CRD	Centre for Research and Dissemination, University of York
f-u	Follow-up
HAART	Highly active antiretroviral therapy
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Hazard ratio
IDU	Injection drug use
IQR	Interquartile range
MD	Mean difference
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
OR	Odds ratio
PI	Protease inhibitors
RNA	Ribonucleic acid
RR	Risk ratio
SVR	Sustained viral response

Abstract

Objectives

Highly active antiretroviral therapy (HAART) is the current standard treatment for individuals co-infected with HIV and hepatitis C. The impact of HAART and antiretroviral (ARV) monotherapy on liver disease in this population is unclear. This systematic review aimed to evaluate the effect of HAART and ARV monotherapy on liver disease progression and liver-related mortality in individuals co-infected with HIV and hepatitis C, including in patients with haemophilia.

Methods

MEDLINE and EMBASE bibliographic databases were searched up to June 2014 for comparative studies. A systematic review on the association between HAART and/or ARV monotherapy and liver disease progression and liver-related mortality was conducted. Study quality was assessed using a modified version of the Newcastle-Ottawa scale and the results were synthesised narratively and by meta-analysis.

Results

Thirteen cohort studies were included. In analyses that adjusted for potential confounding factors (such as age, sex and liver disease severity), the risk of liver-related mortality was reduced by around approximately 70% in patients receiving HAART when compared to untreated patients. The results were similar in unadjusted analyses. A subgroup analysis, in which most patients had haemophilia, also found that HAART was associated with a reduction in liver-related mortality.

For other outcomes where meta-analyses could not be performed, the results were less consistent. Some studies suggested a benefit of HAART in reducing the incidence or slowing the progression of liver disease, fibrosis and cirrhosis, while others showed no evidence of benefit or harm, compared with no antiretroviral therapy.

Limitations

Only observational studies were identified, so the risks of bias and confounding cannot be excluded. Liver disease outcomes could not be pooled statistically, thereby limiting the strength of the findings on liver-disease progression.

Conclusions

The use of HAART was associated with significantly reduced liver-related mortality in patients co-infected with HIV and HCV. Evidence of an association between HAART and/or ARV monotherapy use and reduced liver-disease progression was less clear, but there was no evidence to suggest that the absence of antiretroviral therapy was preferable. Further research is required on the differential effects of HAART regimens, and on the mechanisms by which HAART reduces liver-disease mortality.

Executive summary

Background

Hepatitis C is an infectious liver disease, caused by the hepatitis C virus (HCV). Most individuals infected in Britain now acquire the virus through unsterile drug injection. Before an effective blood donor screening test was introduced in the UK in 1991, many people were infected through blood transfusion or therapy with medical products manufactured from donated human blood.

Due to shared routes of transmission, many patients infected with HIV also become infected with HCV. Cirrhosis can develop in patients with chronic HCV infection, with complications including end-stage liver disease and hepatocellular carcinoma, which are important causes of mortality. HIV co-infection has been found to accelerate the progression of chronic hepatitis C to cirrhosis and end-stage liver disease. The widespread use of antiretroviral therapy in developed countries has resulted in HIV-infected patients living longer, and so chronic HCV infection has become an important cause of liver disease in co-infected individuals.

The current standard treatment for individuals co-infected with HIV and HCV is a combination of at least three antiretroviral drugs, often called 'highly active' or 'combination' antiretroviral therapy (HAART). It has been suggested that HIV viral suppression and immune reconstitution, caused by HAART, could affect the rate of HCV-fibrosis progression. The most recent systematic review, however, found limited and inconsistent evidence on the association between antiretroviral therapy and liver-disease outcomes; it was published in 2007 and is now out of date.

Objectives

This systematic review aimed to evaluate the effect of HAART and ARV monotherapy on liver-disease progression and liver-related mortality in individuals co-infected with HIV and hepatitis C, including in patients with haemophilia.

Methods

This systematic review was conducted following the general principles recommended in the *Guidance for Undertaking Reviews in Health Care*, produced by the Centre for Reviews and Dissemination, and the reporting guidance of the PRISMA statement.

Literature search

MEDLINE and EMBASE databases were searched in June 2014 for studies published in English. No date restrictions and no study design filters were applied. The reference list of a previous systematic review on the effect of antiretroviral therapy on liver disease was checked for further relevant studies.

Selection criteria

Studies were eligible for inclusion if they evaluated the effect of HAART and/or ARV monotherapy on liver-related mortality and liver-disease progression in patients co-infected with HIV and HCV. Studies had to include a comparison group of individuals who did not receive or had discontinued HAART and/or ARV monotherapy, and had to measure exposure to treatment and outcome at more than one point in time (for example, cohort

and case-control studies). Studies examining HCV viral load, or transaminase/aminotransferase only, were excluded.

Appraisal and synthesis of the evidence

The quality of the included studies was assessed using a modified version of the Newcastle-Ottawa scale. Where possible and where studies provided sufficient data, these were pooled in meta-analyses. Otherwise, the results were synthesised narratively.

Results

Quantity and quality of studies

Thirteen cohort studies were included in the review. No randomised studies were identified. Most studies were conducted in Europe; none were conducted in the UK. Most patients had a history of injection-drug use, and only two studies were primarily of patients with haemophilia. All studies evaluated the effect of HAART, and about half of them also reported data for patients receiving ARV monotherapy only. Seven studies reported data on liver-related mortality, of which six were included in a meta-analysis. Nine studies reported on liver-disease progression and were summarised narratively.

The risk of confounding, due to failing to account for key confounding factors such as age, sex and liver-disease severity, was the most frequent quality concern in the included studies. The risk of bias associated with participant selection was generally considered to be either low or unclear, and the risk of bias associated with outcome measurement was mostly low.

Summary of effectiveness

HAART was associated with a substantial reduction -around 60-70% - in liver-related mortality in HIV/HCV co-infected patients, depending on the analysis performed. In analyses that adjusted for potential confounding factors (such as age, sex and liver-disease severity), HAART was associated with a substantial reduction in liver-related mortality, with a hazard or odds ratio (HR/OR) of around one-third of that in untreated patients (HR/OR 0.31, 95% CI 0.14 to 0.70). The results were similar in unadjusted analyses (RR 0.40, 95% CI 0.29 to 0.55).

A subgroup analysis including nearly all patients with haemophilia also found that HAART reduced liver-related mortality, but there were too few data to provide an accurate estimate and to determine if the effect differed from that in other populations.

For other outcomes where meta-analyses could not be performed, the results were less consistent. Some studies suggested a benefit of HAART in reducing the incidence or slowing the progression of liver disease, fibrosis and cirrhosis, while others showed no evidence of benefit or harm, compared with no HAART/ARV monotherapy.

Discussion

Strengths and limitations

Ideally, a review of treatment effectiveness should be based on randomised studies to reduce the risk of bias. However, no randomised trials comparing HAART/ARV monotherapy with no antiretroviral therapy were identified. Therefore, observational studies were included, and although attempts were made to address the risk of confounding in the analyses, the potential for bias cannot be excluded. A strength of this

systematic review was the statistical pooling of studies (where possible) on the association between HAART and liver-disease progression in patients co-infected with HIV and HCV. There were too few studies to conduct meta-regression or further subgroup analyses to explore the moderating effects of several relevant factors, including age, liver-disease severity, time since HCV/HIV infection and alcohol abuse.

Generalisability of the findings

In most studies, most patients had a history of injection drug use (IDU), or their drug use was not reported. Patients with a history of IDU are likely to differ in significant ways from those with haemophilia. Although the results from studies of patients with haemophilia did not differ significantly from those from other populations, the unique circumstances of patients with haemophilia should be considered when interpreting the results from patients without haemophilia.

Most studies included in the review were conducted in Europe; none was from the UK. Potential differences in the management of HIV/HCV co-infection across different health systems may limit the applicability of the review findings to co-infected populations in the UK.

Conclusions

The use of HAART was associated with significantly reduced liver-related mortality in patients co-infected with HIV and HCV. Evidence of a positive association with liver-disease progression was less clear, but there was no evidence to suggest that the absence of HAART or ARV monotherapy was preferable.

Implications for policy and clinical practice

This review supports the use of HAART in patients co-infected with HIV and HCV, and suggests that it has benefits on liver-related mortality in addition to its known impact on HIV-related morbidity and mortality.

Further research

Given the common use of HAART in HIV management, a systematic review on the acute and chronic effect of different HAART regimens would be useful. Similarly, a systematic review addressing patients' experiences of HAART, for example acceptance of the intervention, would be useful. Further research is required on the impact of HAART on liver-disease progression and the mechanisms by which liver-disease mortality is reduced with HAART.

1. Background

Hepatitis C is an infectious liver disease caused by the hepatitis C virus (HCV). Hepatitis C infections occur if the virus is able to enter the bloodstream and reach the liver. Today, most individuals infected in Britain acquire the virus through unsterile drug injecting practices. HCV is also prevalent in men who have sex with men, and its incidence is rising in this population (Bradshaw et al. 2013). Historically, before an effective blood-donor screening test was introduced in the UK in 1991, many people were infected through blood transfusion or therapy with medical products manufactured from donated human blood. It is estimated that blood transfusion resulted in approximately 23,500 transmissions during the 1970s and 1980s in England (Soldan et al. 2002), and around 28,000 in the UK (Department of Health 2011). More than 4,600 patients with bleeding disorders were infected by treatment with HCV-contaminated plasma products. Since 2004, those surviving patients who acquired chronic HCV infection through contaminated blood, blood products and tissue transplantation have received financial support via the Skipton Fund.¹ This provides patients infected with chronic HCV through NHS blood products with compensation payments according to prescribed criteria (House of Commons Hansard 2013). In addition, the Macfarlane Trust was set up in 1988 by the British Government to support people with haemophilia who were infected with HIV as a result of contaminated NHS blood products.² The Eileen Trust has provided support for people infected with HIV since 1993.³

1.1 The natural history of hepatitis C infection

Two distinct stages of HCV infection are recognised; acute and chronic. Acute hepatitis occurs within six to eight weeks of infection and may or may not be symptomatic. The virus may clear from the bloodstream in 15% to 25% of those with acute HCV who are not treated during this period. Lack of viral clearance results in chronic HCV, which is marked by the presence of HCV ribonucleic acid (RNA) for more than six months (Micallef et al 2006). Cirrhosis develops in around 20% of patients with chronic infection over approximately 15 to 20 years, and the major direct complications are end-stage liver disease and hepatocellular carcinoma. Around 55% of patients treated with current therapy (pegylated interferon and ribavirin) may achieve sustained viral response (SVR) (Fried et al 2002; Manns et al 2001; Shepherd et al 2007).

1.2 Hepatitis C and HIV co-infection

Due to shared routes of transmission, many patients infected with HIV also acquire infection with hepatitis C virus (HCV); this occurs in more than 80% of injection drug users and individuals with haemophilia (Hayashi et al. 1991; Rumi et al. 1990). Although the role of hepatitis C in the progression of HIV disease is partly unclear (Daar et al. 2001; Sulkowski et al. 2002), HIV infection has been found to accelerate the progression of chronic hepatitis C to cirrhosis and end-stage liver disease (Kramer et al. 2007). Among patients with haemophilia, there is a four- to eight-fold increase in progression to end-

¹ www.skiptonfund.org

² www.macfarlane.org.uk

³ <http://www.aidsmap.com/org/8636/page/1411896/>

stage liver disease in HIV-positive individuals, compared with those who are HIV-negative (Goedert et al. 2002; Graham et al. 2001; Ragni and Belle 2001). This risk may be increased by factors such as hepatitis B infection, alcohol use and increasing duration of HCV infection (Ragni and Belle 2001). HCV-related liver disease is an important cause of death in co-infected individuals (Bruno et al. 2007; Sulkowski et al. 2007), including those with haemophilia (Qurishi et al. 2003). Liver-related mortality is comparatively low in patients with HIV infection alone (Eyster et al. 1993; Rockstroh et al. 1996; Soriano et al. 1999).

1.3 Antiretroviral therapy in patients co-infected with hepatitis C and HIV

The first effective therapy against HIV was a nucleoside reverse transcriptase inhibitor (NRTI), which was approved by the US Food and Drug Administration in 1987. In 1996, a more effective three-drug therapy combining two NRTIs with a new class of antiretrovirals - protease inhibitors - was incorporated into clinical practice. The current standard treatment consists of a combination of at least three drugs (often called 'highly active', 'combination' antiretroviral therapy, or HAART). The widespread use of antiretrovirals in developed countries has substantially reduced mortality in HIV-infected individuals. Partly because of HIV-infected patients' ability to live longer, chronic HCV infection, which generally progresses to clinical disease over decades, has become an important cause of liver disease in co-infected individuals (Bica et al. 2001). A Canadian cohort study of HIV-infected patients with haemophilia found that following the introduction of HAART, the proportion of deaths due to acquired immune deficiency syndrome (AIDS) had decreased, while the proportion of deaths due to liver disease had increased (Arnold et al. 2006).

Antiretroviral therapy is currently recommended in co-infected patients, including those with cirrhosis, by national guidelines, including the British HIV Association and US National Institutes of Health (Williams et al. 2014). It has been suggested that the HIV viral suppression (Brau et al. 2006) and immune reconstitution (Lange and Lederman 2003) possible with HAART are critical factors that positively affect the rate of HCV fibrosis progression. The most recent published systematic review found limited and inconsistent evidence on the association between antiretroviral therapy and liver-disease outcomes (Kramer et al. 2007). Some studies have reported that HAART may adversely affect hepatitis C outcomes by increasing HCV viral load, liver toxicity and fibrosis progression (Bonacini 2004; Sulkowski 2005; Verma 2006; Verma et al. 2006). It is possible that HAART can attenuate liver-disease progression through the reversal or prevention of HIV-related immunosuppression, but it is also plausible that antiretroviral use may exacerbate liver disease (Ragni et al. 2009). Significant liver enzyme elevations (grade 3 or 4 hepatotoxicity) are observed in approximately 5% to 10% of people taking a new HAART regimen. In addition, the incidence of HAART-associated liver toxicity is approximately three times greater in HIV/HCV-co-infected individuals than in those without hepatitis C (Benhamou et al. 2001; Verma et al. 2006), and increases in hepatitis C viral loads have been observed in patients with haemophilia receiving HAART (Ragni and Bontempo 1999). Although many liver enzyme elevations resolve even when HAART is maintained (Brau et al. 2006), the effect of HAART on the progression of HCV-related liver disease is uncertain (Kramer et al. 2007).

A review published in 2007 (Kramer et al. 2007) addressed the association between antiretroviral therapy and liver disease outcomes, but is now out of date, and therefore, an up-to-date systematic review of the available evidence is needed.

1.4 Aims

This systematic review aimed to evaluate the effect of HAART and ARV monotherapy on liver-disease progression and liver-related mortality in individuals co-infected with HIV and hepatitis C, including in patients with haemophilia.

2. Methods

A systematic review was conducted following the general principles recommended in the *Guidance for Undertaking Reviews in Health Care* (Centre for Reviews and Dissemination 2009), and the reporting guidance of the PRISMA statement (Moher et al. 2009). The review was carried out between 13 June and 31 August 2014. The short timeframe limited our ability to search for grey literature, and we limited study inclusion to those published in English.

2.1 Search strategy

A search strategy was initially developed for MEDLINE (Ovid SP). Various text words, synonyms and subject headings were identified by scanning key papers identified at the beginning of the project, by discussion with the review team and through the use of database thesauri. The final searches included terms such as ‘hepatitis C’, ‘HIV’, ‘antiretroviral therapy’, and ‘liver disease’.

MEDLINE and EMBASE electronic databases were searched up to June 2014. The MEDLINE search strategy was adapted for EMBASE. No date restrictions and no study design filters were applied. Only studies published in English were considered, and conference abstracts were excluded. The reference list of a relevant systematic review identified by the initial searches was checked for further relevant studies (Kramer et al. 2007). The full search strategies and results for each database can be found in Appendix 2. Records were initially managed within an EndNote library (EndNote version X7, Thomson Reuters, CA, USA).

2.2 Selection criteria

The abstracts of studies identified by the searches were assessed for inclusion using the criteria outlined below. For records of potential relevance, the full papers were also assessed. Titles and abstracts were screened by one reviewer using EndNote X7 software. Full papers were assessed by two reviewers independently, with disagreements resolved by discussion. Studies were included in the review if they met the criteria listed below.

2.2.1 Participants

Studies of patients co-infected with HIV and chronic HCV were included. HIV and HCV may be managed differently in developing countries; therefore, studies conducted in developing countries were excluded.

2.2.2 Interventions

Any ARV monotherapy or any combination of antiretrovirals was considered to be eligible, including entry/fusion inhibitors, nucleoside reverse transcriptase inhibitors (NRTIs)/nucleoside/ nucleotide analogues, non-nucleoside reverse transcriptase inhibitors (NNRTIs), integrase inhibitors, protease inhibitors (PI) and chemokine receptor (CCR5) antagonists.

2.2.3 Comparator

Studies had to include comparison patients who did not receive or had discontinued HAART/ARV monotherapy.

2.2.4 Outcomes

Liver-related mortality and liver-disease progression were the two outcomes of interest. Liver-disease progression included: progression to/of fibrosis and cirrhosis; compensated liver disease; liver decompensation (ascites, encephalopathy, bleeding varices and/or jaundice); end-stage liver disease; and hepatocellular carcinoma. Liver disease progression outcomes had to be measured using appropriate methods, such as liver biopsy or a validated non-invasive method. Studies examining HCV viral load, or transaminase/aminotransferase only were excluded. Data had to be presented as, or allow the calculation of, effect estimates such as risk ratio (RR), odds ratio (OR), hazard ratio (HR), or mean difference (MD).

2.2.5 Study design

Ideally, a review of treatment effectiveness should include long-term prospective trials with random allocation of patients to the intervention groups. Random allocation is an effective method that reduces the risk of bias and confounding (Bland 2000). However, randomised trials comparing HAART and/or ARV monotherapy with no antiretroviral therapy are not possible, primarily for ethical reasons (HAART is widely accepted for reducing HIV related morbidity and mortality). Therefore, this review included the best available non-randomised evidence.

Comparative studies that measured exposure to treatment and outcome at more than one point in time, such as cohort and case-control studies, were eligible for inclusion. Studies that measured treatment and outcome at the same point in time were excluded since they were not deemed suitable for measuring disease progression. Therefore, case series, correlation and cross-sectional studies (NICE 2006) were excluded.

2.3 Data extraction

Key study details and patient characteristics, such as age, sex, baseline liver-disease severity, mode of HCV/HIV infection, HIV/HCV treatment regimen, HIV and HCV disease history, and concomitant treatments, were extracted using EPPI-Reviewer (Thomas et al. 2010). Outcomes were extracted into a standard Excel spreadsheet. Where outcomes were reported with different levels of adjustment (for example, adjusting for age and sex only versus age, sex and time-dependent covariates), the results with the most adjustments were selected.

2.4 Quality assessment of the studies

The risk of bias was evaluated using a modified version of the Newcastle-Ottawa quality assessment tool (Wells et al. [2014]). Three main domains were considered: participant selection, confounding and outcomes. In addition, the relevance of the study participants to the key population of interest for this review (patients with haemophilia) was considered. Further details regarding the quality assessment criteria are reported in Appendix 3.

The data were extracted and study quality was assessed by one reviewer and checked by a second. Study selection was conducted using EndNote X7 software and EPPI-Reviewer. Data extraction was conducted with EPPI-Reviewer and Microsoft Excel. Quality assessment was performed using EPPI-Reviewer.

2.5 Analysis

The results for liver-related mortality and liver-disease progression were pooled in a meta-analysis, if at least two studies reported that outcome and if data were reported consistently enough for analysis to be feasible. Otherwise, the results were summarised in a narrative synthesis. Where meta-analyses were performed, outcomes were pooled using standard random-effects DerSimonian and Laird meta-analyses (1986). Heterogeneity was assessed using I^2 (Higgins and Green 2011). When pooling adjusted odds, or hazard or risk ratios, these were assumed to be equivalent regardless of the specific statistic reported and the covariates that were adjusted for.

Where participants from several studies were recruited from the same cohort and significant overlap was suspected, attempts to contact authors were made, and the data from only one study, with the most reliable reporting, were included in the main analyses. The impact of studies where substantial overlap was suspected, or where only a composite outcome was reported, was explored by including/excluding them from the main analyses (in sensitivity analyses).

Where possible, subgroup analyses including only studies with a large proportion of patients with haemophilia were conducted. Meta-regressions and other subgroup analyses were considered inappropriate due to the small number of studies.

3. Results

3.1 Overview of the evidence

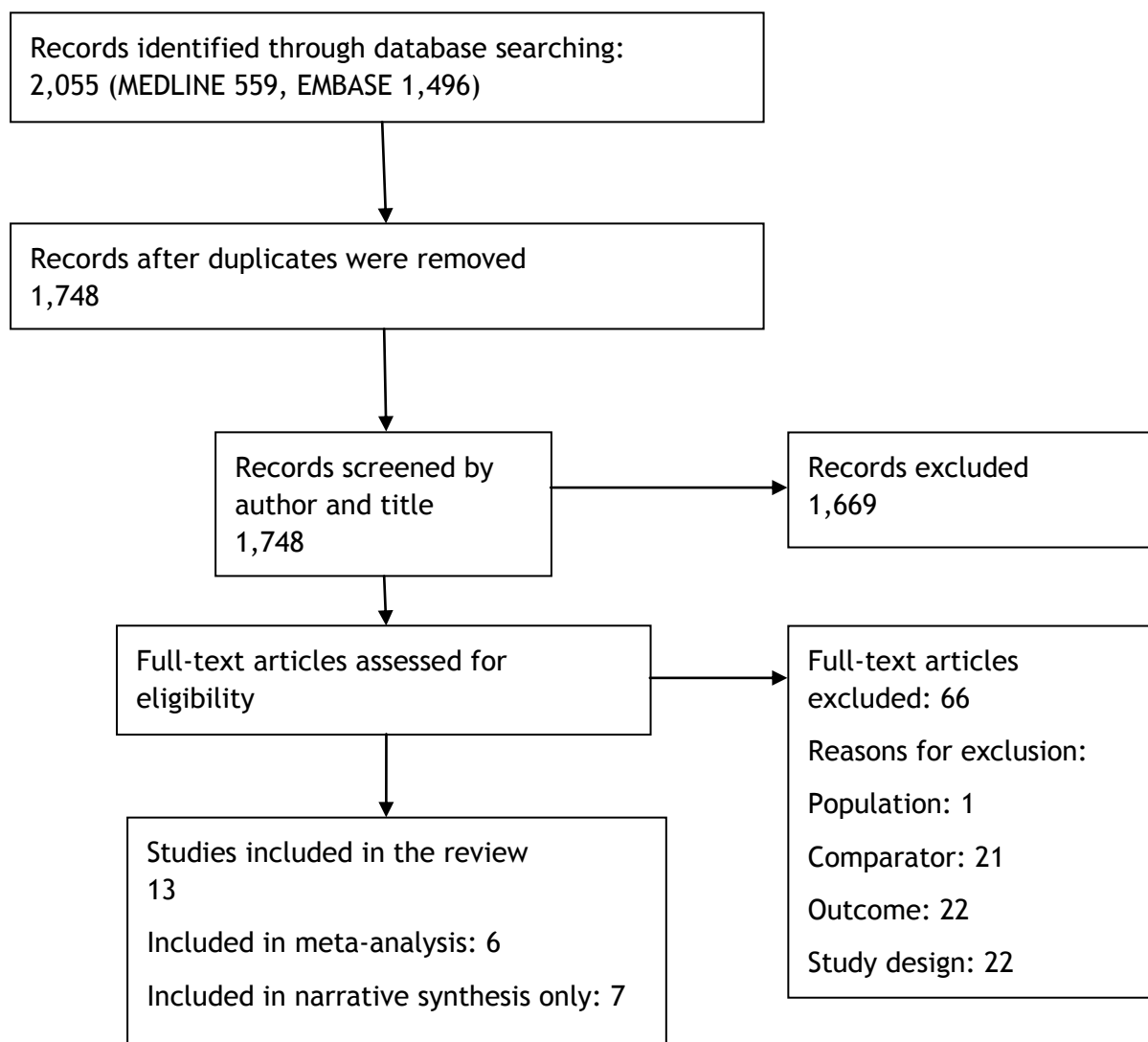
Thirteen studies were included in the review. All were classed as cohort studies, with sample sizes ranging from 36 to 683 participants. Three studies were conducted in the USA. All the other studies were conducted in Europe; none were conducted in the UK. Most patients had a history of injection drug use, and only two studies were primarily of patients with haemophilia. All studies evaluated the effect of HAART, and about half of them also reported data for patients receiving ARV monotherapy only. About half of the studies evaluated the effect of HAART and/or ARV monotherapy on liver-related mortality, and nearly all reported other liver-related outcomes.

From meta-analyses, there was statistically significant evidence that HAART was associated with a substantial reduction in liver-related mortality in HIV/HCV co-infected patients, by around 60-70%, depending on the analysis performed. For other outcomes where meta-analyses could not be performed, the results were more mixed. Some studies suggested a benefit of HAART in reducing the incidence or slowing the progression of liver disease, fibrosis and cirrhosis, while others showed no evidence of benefit or harm.

3.2 Flow of studies

The database searches yielded a total of 1,748 unique titles and abstracts, including all relevant studies that had been included in the previously published systematic review by Kramer et al. (2007). From these references, 79 studies of potential relevance were identified. Based on the full text, 66 studies were rejected, and 13 studies met our inclusion criteria. Of these, six studies were included in the meta-analyses, and seven were summarised in a narrative synthesis only.

Figure 1: Flow of studies



3.3 Quality and assessment of bias of the included studies

The risk of confounding, due to failing to account for key factors, such as age, sex/gender and liver-disease severity, was the most frequent quality concern in the included studies. Five studies provided only unadjusted results on the relevant outcomes and were therefore considered to be at high risk of confounding (Mariné-Barjoan et al. 2004; Mehta et al. 2005; Merchante et al. 2006; Reiberger et al. 2010; Reiberger et al. 2010). Four studies used appropriate methods to adjust for potential confounding and were considered to be at a lower risk of confounding (Limketkai et al. 2012; Macías et al. 2009; Qurishi et al. 2003; Ragni et al. 2009). Four other studies raised concerns because their comparison groups might have included patients exposed to HAART (for example, patients in one comparator group were classed as ‘no HAART’ if they had <80% adherence to HAART, suggesting that they received some HAART) (Giron-Gonzalez et al. 2007). These four studies were, therefore, classed as at moderate risk of confounding (Bruno et al. 2007; Giron-Gonzalez et al. 2007; Macías et al. 2006; Pineda et al. 2009).

How patients were selected for inclusion in the studies was often poorly reported, suggesting that some studies could have introduced bias.^{1, 3-6, 9, 11} In five other studies, the selection methods were insufficiently reported to assess the risk of selection bias.^{2, 7, 8, 10, 13} One study was considered to be at high risk of selection bias.¹²

Most studies measured and reported their outcomes using appropriate clinical methods, and therefore, were classed as at low risk of outcome measurement bias. Only one study was considered to be at high risk of outcome measurement bias, due to limited follow-up.⁷

Two studies reported including a substantial proportion of patients with haemophilia.^{10, 11} In all other studies, most patients had a history of injection drug use (low relevance), or their drug use or likely mode of infection was not reported (unclear relevance).

Further details of the quality criteria and judgments are reported in Table 3.1 and Appendix 3.

Table 3.1: Risk of bias

Study*	Selection bias	Confounding bias	Outcome measurement bias	Relevance
Bruno (2007)	Low	Moderate	Low	Unclear
Giron-Gonzalez (2007)	Unclear	Moderate	Low	Low
Limketkai (2012)	Low	Low	Low	Low
Macías (2006)	Low	Moderate	Low	Low
Macías (2009)	Low	Low	Unclear	Low
Mariné-Barjoan (2004)	Low	High	Low	Low
Mehta (2005)	Unclear	High	High	Low
Merchant (2006)	Unclear	High	Low	Low
Pineda (2009)	Low	Moderate	Low	Low
Qurishi (2003)	Unclear	Low	Low	High
Ragni (2009)	Low	Low	Unclear	High
Reiberger (2010)	High	High	Low	Low
Schiavini (2006)	Unclear	High	Low	Unclear
Total risk of bias	7 low 1 high 5 unclear	4 low 5 high 4 moderate	10 low 1 high 2 unclear	9 low 2 high 2 unclear

*In all the tables, the first author only is specified.

3.4 Characteristics of included studies

3.4.1 Study characteristics

Out of 13 studies, six followed patients prospectively (Giron-Gonzalez et al. 2007; Limketkai et al. 2012; Mehta et al. 2005; Merchante et al. 2006; Pineda et al. 2009; Ragni et al. 2009); the remaining seven studies were classed as retrospective cohorts.

Five studies were conducted in Spain, three in the USA, two in Italy, one in France, one in Germany and one in Austria. There was some overlap across the Spanish cohorts in their recruitment centres and study dates, and it was likely that some participants were included in more than one of these studies. However, we felt that there were sufficient differences in the reporting of outcomes and liver-disease severity to treat them as distinct studies. See Appendix 4 table 6 for further details.

Nearly all the included studies were published after 2005 (end of searches by Kramer et al. 2007), except for three studies which were also included in the review by Kramer et al. (Mariné-Barjoan et al. 2004; Mehta et al. 2005; Qurishi et al. 2003).

Study dates ranged from 1970 to 2011. Six studies were conducted across the pre-post HAART era (before and after 1996) (Limketkai et al. 2012; Macías et al. 2006, 2009; Qurishi et al. 2003; Ragni et al. 2009; Schiavini et al. 2006), including the two studies in which most patients had haemophilia (Qurishi et al. 2003; Ragni et al. 2009). Only one study reported receiving industry funding (Merchante et al. 2006).

All the included studies evaluated the impact of HAART, and seven also included patients treated with ARV monotherapy only. Most patients who received HIV treatment and who were included in cohorts after 1996 received HAART. Where reported, the most common 'base' for HAART was protease inhibitors, followed by nucleoside analogues and NNRTIs. Only one study clearly reported time of HIV treatment initiation, which took place after a first event of decompensation (Bruno et al. 2007). Only one study clearly reported HIV treatment duration, which ranged from 87 to 364 weeks (Macías et al. 2006).

Eight studies reported HAART/ARV monotherapy exposure prior to baseline. All stated that most participants in the intervention group had received HAART and/or ARV monotherapy before the study started (Bruno et al. 2007; Giron-Gonzalez et al. 2007; Limketkai et al. 2012; Macías et al. 2006; Mehta et al. 2005; Merchante et al. 2006; Pineda et al. 2009; Qurishi et al. 2003).

Five studies reported treating between 8% and 92% of their sample with HCV therapy (interferon with or without ribavirin) (Giron-Gonzalez et al. 2007; Macías et al. 2009; Pineda et al. 2009; Ragni et al. 2009; Schiavini et al. 2006), while four stated that no patients received HCV therapy during the study (Macías et al. 2006; Mariné-Barjoan et al. 2004; Qurishi et al. 2003; Reiberger et al. 2010). Liver transplants were reported in only two studies: Ragni et al. (2009) reported that 6% of their participants underwent liver transplant during the study, and Giron-Gonzalez et al. (2007) reported a similarly low rate (8%).

The reason for absence of antiretroviral therapy in the comparison group was only provided in one study; patients included in the no-HAART group in Ragni et al. (2009) were either 'unwilling or died before drugs were available.' Further intervention characteristics are reported in Appendix 4.

Table 3.2: Study characteristics

Author (year)	HAART, ARV monotherapy, or both	Concomitant treatment
Bruno (2007)	HAART only	HCV treatment unknown. None for 33% with genotype 3
Giron-Gonzalez (2007)	HAART only	8% liver transplant
Limketkai (2012)	HAART and/or ARV monotherapy	NR
Macías (2006)	HAART and/or ARV monotherapy	No HCV therapy
Macías (2009)	HAART and/or ARV monotherapy	44% HCV treatment (across groups)
Mariné-Barjoan (2004)	HAART only	No HCV therapy
Mehta (2005)	HAART and/or ARV monotherapy	NR
Merchante (2006)	HAART only	NR
Pineda (2009)	HAART only	43% of total population HCV therapy at follow-up
Qurishi (2003)	HAART and/or ARV monotherapy	No HCV treatment
Ragni (2009)	HAART and/or ARV monotherapy	1% HCV, 6% liver transplant
Reiberger (2010)	HAART only	No HCV treatment
Schiavini (2006)	HAART and/or ARV monotherapy	Interferon 92% across groups (of which 6% had SVR)

NR: Not reported. Further study characteristics can be found in Appendix table 4.

Participant characteristics

Most participants were male (67% to 100% across studies). Only two studies reported including patients with haemophilia. In Qurishi et al. (2003), 81% of patients had haemophilia, and in Ragni et al. (2009), all patients were recruited from a haemophilia clinic. Only three studies reported the participant's age at HIV/HCV infection, or data from which this could be inferred. Age at HIV/HCV infection ranged from birth (in the two studies including patients with haemophilia) (Qurishi et al. 2003; Ragni et al. 2009) to over 26 years (Mariné-Barjoan et al. 2004). Only two studies reported how long participants had been infected with HCV (Mariné-Barjoan et al. 2004; Ragni et al. 2009). Where reported, the median age at HAART/ARV monotherapy initiation ranged from 28 to 45.6 years. Only three studies reported data on ethnicity. Nearly all participants in Ragni et al. (2009) were

Caucasian (96%). Limketkai et al. (2012) and Mehta et al. (2005) included 80% and 85% Black/African American participants respectively.

Baseline liver damage severity varied across the studies. Eight studies included no or few patients with cirrhosis (Limketkai et al. 2012; Macías et al. 2006, 2009; Mariné-Barjoan et al. 2004; Mehta et al. 2005; Ragni et al. 2009; Reiberger et al. 2010; Schiavini et al. 2006); four studies included only patients with compensated cirrhosis at baseline. Two of these tracked liver disease progression from the first event of decompensation (Giron-Gonzalez et al. 2007; Merchante et al. 2006). One reported no symptomatic liver disease at ARV initiation (Qurishi et al. 2003).

Nearly all patients were HCV RNA positive, although two studies reported rates of patients who tested anti-HCV positive only (Giron-Gonzalez et al. 2007; Ragni et al. 2009). Where reported, baseline CD4 cell count ranged from a median of 202 to 460 cells/mm³, and the percentage of patients with current active HBV infection ranged from zero to 17.

Where reported, the percentage of patients abusing alcohol at baseline ranged from 12 to 47. Seven studies reported a percentage of participants with current or past injection drug use of 72 or above. Further participant characteristics are reported in Table 3.3.

Table 3.3: Participant characteristics

Author (year)	Age (years) ¹	% male	HCV %	Comorbidities (%)	Baseline liver disease severity	CD4 cell count (cells/mm ³) at baseline	Current or past substance abuse
Bruno (2007)	Median 37.1 (range 29.3 to 50.3)	90	86	Haemophilia: NR HBV: 10	100% compensated cirrhosis	88% <350	NR
Giron-Gonzalez (2007)	Median 40 (IQR 37 to 43)	89	100 HCV+ ²	NR	100% compensated cirrhosis	Median 261 (IQR 150 to 459)	Alcohol: 46 current IDU: 90
Limketkai (2012)	Median 45.6 (IQR 40.8 to 49.6)	66	100	NR	Mostly no cirrhosis	18% <200. Median 381	Alcohol: 47 current IDU: 76 past
Macías (2006)	Median 23 (at HCV infection) (IQR 19 to 28)	83	100	Haemophilia: NR HBV: 0	Mostly no cirrhosis	NR. At follow-up: median 504 (IQR 343 to 700)	Alcohol: 21 current IDU: 90
Macías (2009)	Mean 37 (SD 5.5)	68	0	NR	No cirrhosis	Median 460 (IQR 319 to 598)	Alcohol: 23 current IDU: 86 current
Mariné-Barjoan (2004)	Median 21 (at HCV infection) (IQR 18 to 26)	67	100 (median duration 15yrs, IQR 12 to 20)	Haemophilia: NR HBV: 0	No cirrhosis	Median 440 (IQR 321 to 612)	Alcohol: 14 current IDU: 72

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Author (year)	Age (years) ¹	% male	HCV %	Comorbidities (%)	Baseline liver disease severity	CD4 cell count (cells/mm ³) at baseline	Current or past substance abuse
Mehta (2005)	Median 44.5 (IQR 40.0 to 47.8)	67	100	Haemophilia: NR HBV: 1	Mostly no cirrhosis	Median 366 (IQR 219 to 528)	Alcohol: 39.5 history IDU: 77% (current or past)
Merchante (2006)	Median 38 (IQR 35 to 41)	86	100	Haemophilia: NR HBV: NR (19 HBsAg +)	100% compensated cirrhosis	Median 202 (IQR 109 to 376)	Alcohol: 46 current IDU: 88 previous
Pineda (2009)	Median 39.9 (IQR 37.1 to 44.1)	87	100	Haemophilia: NR HBV: 6	100% compensated cirrhosis	Median 403 (IQR 255 to 572). HIV contracted between 1982 and 1985 in patients with haemophilia.	Alcohol: 21 IDU: 86 current or previous
Qurishi (2003)	Median 30 (range 23 to 38)	94 to 96	100	Haemophilia: 81 HBV: 6	No symptomatic liver disease	Median CD4 count (x10 ⁹ /L) (IQR): HAART: 0.243 (0.108 to 0.361) ARV monotherapy: 0.279 (0.122 to 0.414) untreated: 0.255 (0.079 to 0.473)	Alcohol: 12 IDU: 15
Ragni (2009)	Mean 39 at follow-up	100	100 HCV ⁺ ²	Haemophilia: 100, of which 92 severe, 89 type A, 11	NA (followed from HCV infection)	Mean: HAART: 351 (SD 56, range 64 to 948)	Alcohol: 12

Author (year)	Age (years) ¹	% male	HCV %	Comorbidities (%)	Baseline liver disease severity	CD4 cell count (cells/mm ³) at baseline	Current or past substance abuse
				type B HBV: 85 HBsAg+ ever		ARV monotherapy: 90 (SD 19, range 4 to 412) untreated: 145 (SD 43, range 2 to 610) (time of measurement unclear)	
Reiberger (2010)	Mean 37 (SD 10)	77	100	Haemophilia: NR HBV: 0	Mostly no cirrhosis, 42% advanced fibrosis	Mean 510 (SD 203): 12% >500; 45% 499 to 201; 43% <200	Alcohol: 29 current IDU: NR
Schiavini (2006)	Median 28 (IQR 26 to 31)	75	100	Haemophilia: NR HBV: 17%	Mostly no cirrhosis	Median 429 (256.5 to 624)	Alcohol: 53 history IDU: NR

¹ At the start of the study, unless otherwise stated; ² Proportion of patients with active HCV not reported

IDU: Injection drug user; IQR: Interquartile range; NR: Not reported; NA: Not applicable

3.5 Findings

Seven studies reported data on liver-related mortality (Bruno et al. 2007; Giron-Gonzalez et al. 2007; Limketkai et al. 2012; Merchante et al. 2006; Pineda et al. 2009; Qurishi et al. 2003; Ragni et al. 2009), and nine studies reported on liver disease progression (Giron-Gonzalez et al. 2007; Macías et al. 2006, 2009; Mariné-Barjoan et al. 2004; Mehta et al. 2005; Pineda et al. 2009; Ragni et al. 2009; Reiberger et al. 2010; Schiavini et al. 2006). Three studies reported data on liver-related mortality and other liver-related outcomes (Giron-Gonzalez et al. 2007; Pineda et al. 2009; Ragni et al. 2009).

3.5.1 Liver-related mortality

Findings from six of the seven studies on liver-related mortality were combined in meta-analyses (Bruno et al. 2007; Giron-Gonzalez et al. 2007; Limketkai et al. 2012; Pineda et al. 2009; Qurishi et al. 2003; Ragni et al. 2009). To avoid the risk of double counting the participants from one study (Giron-Gonzalez et al. 2007), the results from the study by Merchante et al. (2006) were not included in the main analyses; their impact on the pooled estimates was explored in a sensitivity analysis. One study presented its results specifically at one and three years; all the others reported total mortality over the study period (ranging from a median of 20 months to 35 years).

Four out of these seven studies presented analyses adjusted for potential confounding factors, and reported an odds risk or hazard ratio (Giron-Gonzalez et al. 2007; Limketkai et al. 2012; Pineda et al. 2009; Qurishi et al. 2003). Figure 2 presents the forest plot of the meta-analysis of these four studies, assuming that odds, risk and hazard ratios are equivalent. This analysis shows that HAART is associated with a substantial reduction in liver-related mortality, with a hazard/odds ratio of around one-third of that in untreated patients (HR/OR 0.31, 95% CI 0.14 to 0.70). Heterogeneity was high ($I^2=95%$), apparently because of the discordant result between the Qurishi et al. (2003) and the Pineda et al. (2009) studies. The Qurishi et al. study showed a much larger benefit; most participants in this study were patients with haemophilia, whereas in the other studies, most patients had a history of injection drug use.

All six studies included in the meta-analysis presented the numbers of patients with and without liver-related mortality, from which relative risks could be calculated (these relative risks were not adjusted for potential confounders). The forest plot of the meta-analysis of relative risks from these six studies is shown in Figure 3. This analysis shows a clear association in favour of HAART for preventing liver-related mortality (RR 0.40, 95% CI 0.29 to 0.55). The summary effect estimate is similar to that seen in Figure 2, but more precise (as indicated by the narrower confidence intervals). There was no evidence of significant heterogeneity in this analysis ($I^2=24%$).

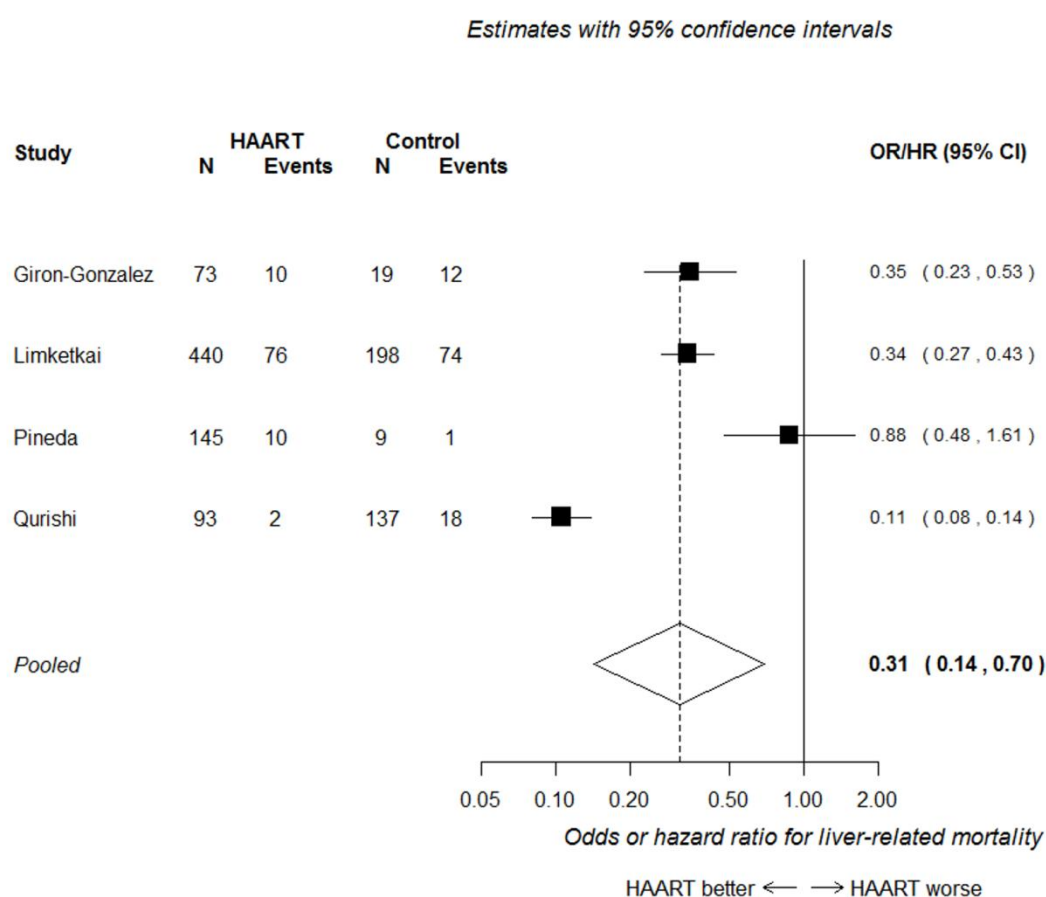
3.5.1.1 Subgroup and sensitivity analyses

Figure 4 presents the forest plot for the two studies conducted primarily in patients with haemophilia (Qurishi et al. 2003; Ragni et al. 2009). This shows that HAART was associated with a reduced risk of liver-related mortality (RR 0.28, 95% CI 0.09 to 0.83), but there were too few data to accurately estimate the effect, and to determine if the effect differed in patients with a history of injection drug use.

One study presented the results only as a Kaplan-Meier survival curve (Merchante et al. 2006). By extracting the data presented in this curve, it was possible to estimate liver-

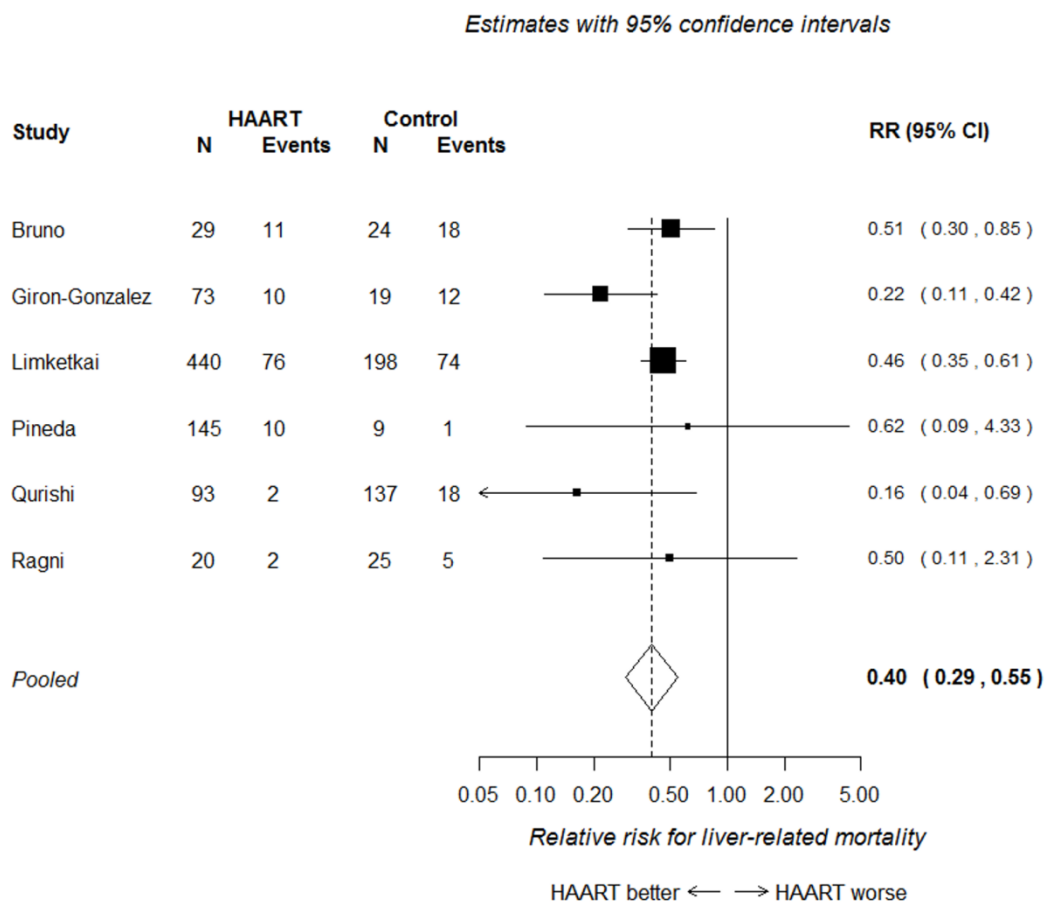
related mortality at 40 months. These data excluded patients with censored (i.e. unknown) disease status. If these censored patients had different disease status (for example, if they dropped out because they could not tolerate HAART) then the results may be biased. The study found that liver-related mortality was significantly lower in patients with compensated cirrhosis on HAART, compared with no treatment (unadjusted HR 0.5; 95% CI 0.3 to 0.9). Adding this study to the meta-analysis did not affect the conclusions, and had a limited effect on the overall results (RR 0.46, 95% CI 0.28 to 0.75). The number of liver-related deaths per group was not reported in the Limketkai study, but at least 63% of the events reported across the two study groups were liver-related deaths. Removing this study from the analyses had only a limited effect on the pooled estimates (RR 0.35, 95% CI 0.21 to 0.57). Further details on liver-related mortality and adjustments are provided in Appendix 5.

Figure 3.2: Hazard ratio of liver-related mortality in HIV/HCV co-infected patients according to HAART use*



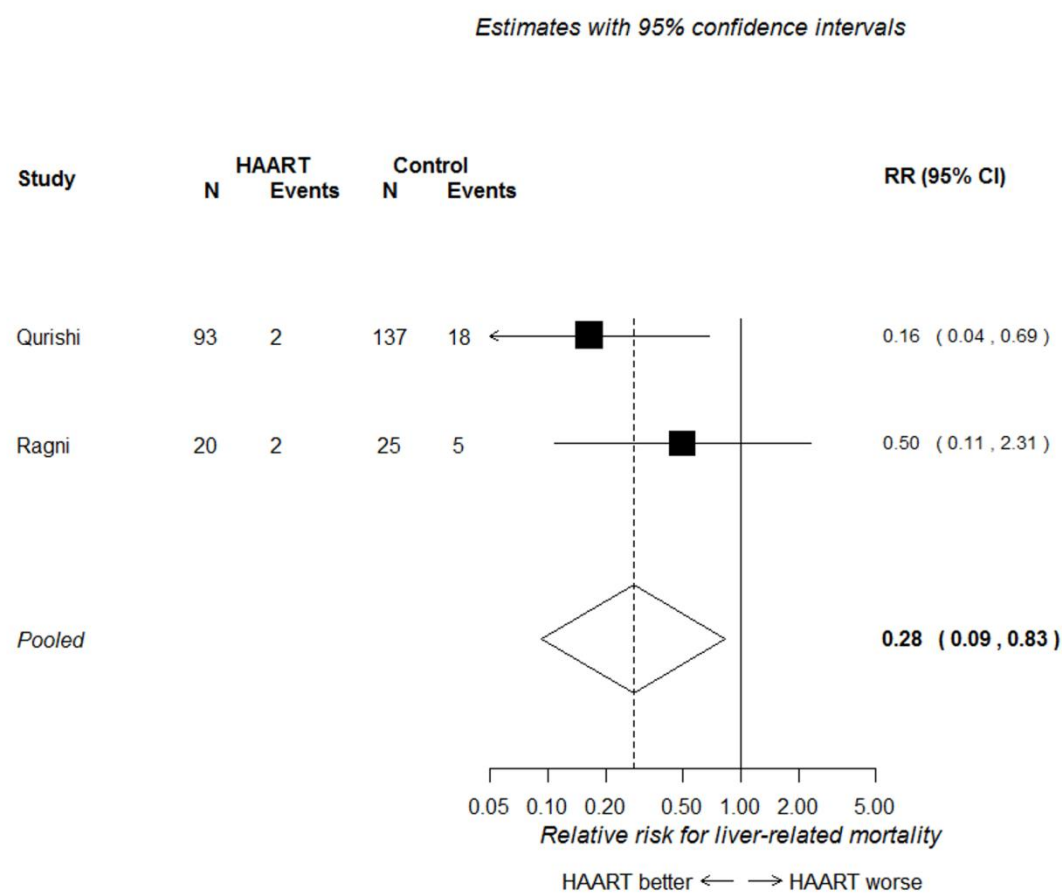
*Only Limketkai et al. (2012) included a small proportion of patients who received ARV monotherapy. All other patients in the intervention group received HAART

Figure 3.3: Unadjusted odds ratios of liver-related mortality in HIV/HCV co-infected patients according to HAART use*



*Only Limketkai et al. (2012) included a small proportion of patients who received ARV monotherapy. All other patients in the intervention group received HAART

Figure 3.4: Unadjusted odds ratios of liver-related mortality in HIV/HCV co-infected haemophiliac patients according to HAART use



3.5.2 Liver disease

Liver disease outcomes were reported too diversely, or in too few studies for meta-analysis. Therefore all nine studies that reported liver disease are summarised in a narrative synthesis (Giron-Gonzalez et al. 2007; Macías et al. 2006, 2009; Mariné-Barjoan et al. 2004; Mehta et al. 2005; Pineda et al. 2009; Ragni et al. 2009; Reiberger et al. 2010; Schiavini et al. 2006). A summary of the findings from these studies is presented in Table 4.

3.5.2.1 End-stage liver disease and decompensation events

Three studies reported data on end-stage liver disease or liver decompensation events (Giron-Gonzalez et al. 2007; Pineda et al. 2009; Ragni et al. 2009). Two of these studies found at least one statistically significant effect in favour of HAART (Giron-Gonzalez et al. 2007; Ragni et al. 2009).

Ragni et al. (2009), investigating the risk of developing end-stage liver disease over 35 years, found no difference between patients with haemophilia receiving HAART and/or ARV monotherapy and untreated patients (RR 1.00, 95% CI 0.37 to 2.71). However, the study found that compared with patients on ARV monotherapy or no treatment, patients receiving HAART survived longer before progressing to end-stage liver disease (30.3 years for HAART, 20.0 years for ARV monotherapy/no treatment; HR 3.14, 95% CI 1.27 to 7.08).

Giron-Gonzalez et al. (2007) and Pineda et al. (2009) both reported on the risk of liver decompensation in patients with liver cirrhosis. Giron-Gonzalez et al. found a significantly lower risk of a new event of decompensation in HAART patients with stable cirrhosis who had experienced decompensation in the past (HR 0.376, 95% CI 0.161 to 0.883). However, no statistically significant difference was found in the subgroup of patients with no previous decompensation at baseline. Similarly, Pineda et al. found no significant difference between HAART and no treatment in the risk of decompensation in patients with cirrhosis.

3.5.2.2 Advanced fibrosis or cirrhosis, and necroinflammatory activity

Only one study reported on the odds of advanced fibrosis or cirrhosis. Mehta et al. (2005) found no statistically significant association between HAART or ARV monotherapy and this outcome in patients with less severe or no fibrosis. ARV monotherapy and HAART were both associated with lower necroinflammatory activity compared with untreated individuals at follow-up, but the association was only statistically significant for the HAART group (OR 0.27, 95% CI 0.14 to 0.5).

3.5.2.3 Fibrosis progression

Five studies reported on liver damage, expressed as fibrosis progression, in patients with no cirrhosis at baseline (Macías et al. 2006, 2009; Mariné-Barjoan et al. 2004; Reiberger et al. 2010; Schiavini et al. 2006). Of these, three reported the odds of fibrosis progression (dichotomous outcome) (Macías et al. 2006, 2009; Schiavini et al. 2006), and three reported the progression rate (continuous outcome) (Macías et al. 2006; Mariné-Barjoan et al. 2004; Reiberger et al. 2010). One study reported both continuous and dichotomous outcomes (Macías et al. 2006).

Of the three studies that reported the odds of fibrosis progression, only one reported a statistically significant difference between intervention and control. Macías et al. (2006) found significantly lower odds of liver fibrosis progression, over up to 49 years, in patients on HAART with protease inhibitors (OR 0.4, 95% CI 0.2 to 0.7) and in patients who switched from a protease inhibitors-based regimen to efavirenz during their treatment (OR 0.3, 95% CI 0.1 to 0.7), but not with other regimens. Macías et al. (2009) and Schiavini et al. (2006) found no significant association between HAART/ARV monotherapy and fibrosis progression.

Of the three studies that reported fibrosis progression rates, two found a difference in favour of HAART (Macías et al. 2006; Mariné-Barjoan et al. 2004), and one found no difference between HAART and no treatment (Reiberger et al. 2010). Macías et al. (2006) found slower median rates of fibrosis progression in patients treated with HAART, compared with no treatment, regardless of the regimen used. However, the difference was only statistically significant for some regimens (zidovudine/lamivudine and stavudine/lamivudine). Mariné-Barjoan et al. (2004) found a slower mean rate of fibrosis progression, over approximately 15 years, in patients taking HAART at follow-up, but the difference did not reach statistical significance. Reiberger et al. (2010) found no difference in fibrosis progression rate and time to cirrhosis, over 25 years, between HAART and no treatment. Further details are reported in Table 3.4.

Table 3.4: Liver disease progression: study results

	Intervention	Outcome	Follow-up duration	Effect estimate	Statistically significant? ¹	Adjustments
End-stage liver disease and decompensation events						
Giron-Gonzalez (2007)	HAART	Decompensation (subgroup with previous decompensation at baseline)	Median 20 months (IQR 12 to 28)	HR 0.376 (95% CI 0.161 to 0.883)	Yes. Favours treatment	Liver disease severity
Giron-Gonzalez (2007)	HAART	Decompensation (subgroup without previous decompensation at baseline)	Median 20 months (IQR 12 to 28)	NR	No (p=0.93)	None
Pineda (2009)	HAART	Decompensation	Mean 36 months (SD 27), range 1 to 131 months	RR 1.06 (95% CI 0.30 to 3.71)	No (p=0.45)	None
Ragni (2009)	HAART and ARV monotherapy	ESLD	Up to 35 years	RR 1.00 (95% CI 0.37 to 2.71)	No	None
Ragni (2009)	HAART ²	Time to ESLD	Up to 35 years	HR 3.14 (95% CI 1.27 to 7.08) (30.3 vs. 20.0 Years)	Yes (p=0.04). Favours treatment	Multivariate (covariates NR)

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	Intervention	Outcome	Follow-up duration	Effect estimate	Statistically significant? ¹	Adjustments
Advanced fibrosis, cirrhosis and necroinflammatory activity						
Mehta (2005)	ARV monotherapy	Advanced fibrosis or cirrhosis ³	Median 5 years (IQR 2.9 to 7.5)	OR 0.61 (95% CI 0.18 to 2)	No	None
Mehta (2005)	HAART	Advanced fibrosis or cirrhosis ³	Median 5 years (IQR 2.9 to 7.5)	OR 0.92 (95% CI 0.48 to 1.8)	No	None
Mehta (2005)	ARV monotherapy	Necroinflammatory activity ⁴	Median 5 years (IQR 2.9 to 7.5)	OR 0.39 (95% CI 0.1 to 1.2)	No	None
Mehta (2005) ⁷	HAART	Necroinflammatory activity ⁴	Median 5 years (IQR 2.9 to 7.5)	OR 0.27 (95% CI 0.14 to 0.5)	Yes. Favours treatment	None
Liver fibrosis progression (dichotomous)						
Macías (2009)	HAART and ARV monotherapy	Liver fibrosis progression ⁵	3 years	OR 0.94 (95% CI 0.67 to 1.33)	No	Age, undetectable HIV viraemia, genotype 3, baseline ALT, baseline necroinflammatory activity, time between liver biopsies, HCV treatment response
Schiavini (2006)	HAART and ARV monotherapy	Liver fibrosis progression ⁶	Median 54 months (IQR)	OR 2.5 (95% CI 0.64 to 9.65)	No	None

	Intervention	Outcome	Follow-up duration	Effect estimate	Statistically significant? ¹	Adjustments
			50 to 86)			
Macías (2006)	HAART with PI	Liver fibrosis progression ⁵	Up to 49 years	OR 0.4 (95% CI 0.2 to 0.7)	Yes (p=0.001). Favours treatment	Age at infection, CD4 count
Macías (2006)	HAART with PI switched to efavirenz	Liver fibrosis progression ⁵	Up to 49 years	OR 0.3 (95% CI 0.1 to 0.7)	Yes (p=0.003). Favours treatment	Age at infection, CD4 count
Liver fibrosis progression (continuous)						
Macías (2006)	HAART with: NVP; or efavirenz; or with PI switched to NVP	Fibrosis progression rate ⁷	Up to 49 years	Median rate 0.087 to 0.115 (vs. 0.134 without HAART)	No	None
Macías (2006)	HAART with zidovudine/ lamivudine, or with stavudine/ lamivudine	Fibrosis progression rate ⁷	Up to 49 years	Median rate 0.107 and 0.112 (vs 0.134 without HAART)	Yes (p≤0.007). Favours treatment	None
Mariné-Barjoan (2004)	HAART	Fibrosis progression rate ⁷	Median 15 years	Mean difference -0.06 (95% CI -0.14 to 0.01)	No	None
Reiberger (2010)	HAART	Fibrosis progression rate ⁷	Mean 24 to 25 years	Mean difference	No (p=0.59)	None

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	Intervention	Outcome	Follow-up duration	Effect estimate	Statistically significant? ¹	Adjustments
				0.01 (95% CI - 0.01 to 0.04)		
Reiberger (2010)	HAART	Time to cirrhosis from initial HCV exposure	Mean 24 to 25 years	Mean difference -1.00 (95% ci -7.26 to 5.26)	No (p=0.59)	None

¹ p<0.05 threshold; ² Compared with ARV monotherapy and no ARV combined; ARV monotherapy patients formed 62% of the comparator group in this analysis. ³ Ishak score ≥F3. ⁴ Modified Hepatic Activity Index (MHAi) ≥5. ⁵ At least 1 Scheuer stage (scale 0 to 4) (modified Knodell-Ishak). ⁶ ≥1 Knodell-Ishak stage increase between two biopsies spaced by at least one year. ⁷ METAVIR Fibrosis stage (0 to 3)/length of HCV infection

PI: protease inhibitors; NVP: nevirapine; ESLD: end-stage liver damage

4. Discussion

4.1 Summary of findings

This systematic review aimed to evaluate the effect of HAART and ARV monotherapy on liver-disease progression and liver-related mortality in patients co-infected with HIV and hepatitis C.

Thirteen cohort studies met the inclusion criteria for this review. All studies evaluated HAART, and about half also included patients on ARV monotherapy. Seven studies reported data on liver-related mortality, of which six were included in a meta-analysis. Nine studies reported other liver-disease-related outcomes, which were reported in a narrative synthesis. In most studies, most patients had a history of injection drug use; in two studies, all or most patients had haemophilia.

Most studies were at a moderate-to-high risk of confounding. The risk of bias associated with participant selection was generally considered to be either low or unclear, and the risk of bias associated with outcome measurement was mostly low.

HAART was found to be associated with a substantial reduction in liver-related mortality, with a chance/hazard ratio of around one-third of that in patients not receiving treatment. The pooled estimates from unadjusted analyses also showed a clear association in favour of HAART for preventing liver-related mortality. A subgroup analysis, in which nearly all patients had haemophilia, also found that HAART was associated with reduced liver-related mortality, but there were too few data to provide an accurate estimate, and to determine if the effect differed from that in other populations.

The findings for other liver-related outcomes were less consistent. One study found a statistically significant lower risk of repeated decompensation in patients on HAART. Another study found no difference between treated and untreated patients in the risk of decompensation, but it found that patients with haemophilia receiving HAART progressed significantly less rapidly to end-stage liver disease, compared with untreated patients. One study found no statistically significant association between HAART and the odds of developing advanced fibrosis or cirrhosis in patients with less severe or no fibrosis. Only two of the five studies that estimated liver-fibrosis progression found a statistically significant result, which favoured HAART. No studies reported that a lack of treatment was associated with significantly better liver-disease outcomes.

4.2 Strengths and limitations of the review

This systematic review was conducted following the general principles recommended in Centre for Reviews and Dissemination (2009) *Guidance for Undertaking Reviews in Health Care*, and the reporting guidance of the PRISMA statement Moher et al. 2009). Study quality and the risk of bias were assessed systematically and considered when interpreting the results. Rigorous methods were used to minimise reviewer bias and error. Wherever possible, data on the treatment effects in individual studies were extracted or calculated, even where quantitative synthesis was not undertaken.

Only English-language studies were included, so it is possible that studies published in languages other than English were missed. The fact that only published studies were

considered means that the risk of publication bias, where studies with statistically significant results are more likely to be published, cannot be excluded.

Bibliographic searches identified only one previous systematic review of direct relevance. This review, which searched for studies up to 2005, reported limited and inconclusive evidence on the association between ARVs and liver disease. The systematic review reported here has identified significantly more relevant cohort studies, most of which were published after 2005. Therefore, this review presents a valuable update of the evidence on the association between HAART/ARV monotherapy and liver-disease progression in patients co-infected with HIV and HCV.

Liver disease outcomes were reported too diversely, or in too few studies for statistical pooling. This was unfortunate as several of the included studies had relatively few participants and may have been underpowered to identify significant effects on liver disease. This limits the strength of the findings on liver-disease progression.

Most studies on liver-related mortality were pooled in a meta-analysis. Adjusted and unadjusted results were pooled separately to address the limitations associated with the risk of confounding.

There were too few studies to conduct meta-regression or further subgroup analyses to explore the moderating effects of several relevant factors, including age, liver-disease severity, baseline CD4 count, time since HCV/HIV infection and alcohol abuse.

4.3 Limitations of the evidence and uncertainties

Ideally, survival should be assessed in a long-term prospective study, with randomised allocation of patients to the treatment groups. However, no randomised controlled trials were identified and all the included studies were observational. Nearly half of the studies did not attempt to adjust for potential confounders, such as age and sex. In those studies that did adjust, the factors accounted for varied across studies. For instance, only two studies controlled for alcohol misuse in their analyses. As mentioned above, attempts were made to address the risk of confounding in the analyses, but given the varied level of adjustment in the studies, the risk of confounding should not be ruled out, even for those studies classed as being at a lower risk of bias due to better adjustment.

The studies might have been affected by a survivorship bias if patients in the treatment group who survived long enough to receive HAART/ARV monotherapy had slower HCV progression, and therefore may have had better HCV-related outcomes (Kramer et al. 2007). The use of a time-dependent variable or Cox proportional hazards modelling, taking HCV duration or progression into account, might have remedied this bias. However, no studies reported using this technique. On the other hand, it is possible that comparison groups had levels of immunosuppression that were considered sufficiently high for their HIV treatment to be delayed, following treatment guidance (Brook et al. 2010; Nuñez 2005; Williams et al. 2014). In this case, patients in the treatment group may in fact have had poorer health at treatment initiation, and may therefore have been more vulnerable and prone to liver-disease progression. It is also possible that co-infected patients, who did not survive before the advent of ARV monotherapy, died of non-liver-related causes. Unfortunately, there were insufficient data on the characteristics of the study participants at baseline to support or reject these assumptions.

The reasons for not receiving HAART/ARV monotherapy were generally not reported. However, given that HIV treatment was likely to have been recommended to most HIV/HCV co-infected patients, particularly those with a high viral load, the reasons for not receiving treatment were likely to be influenced by patient choice. For example, those receiving HAART/ARV monotherapy might have been less likely to be active injection drug users, such as ex-injection drug users on methadone programmes who acquired HIV/HCV through this route, and might have had different lifestyles, such as less alcohol and substance abuse, compared with those who did not receive treatment. The reporting of baseline differences between treatment and comparator groups was variable and limited in several studies. Although no studies reported significant differences between groups, such as in current alcohol, injection drug or other substance abuse, and although some cohorts adjusted for these variables in their analyses, it is still possible that those who received HAART/ARV monotherapy were different from those who did not for reasons that may have influenced their liver-related outcomes.

There was significant evidence of a positive effect on liver disease favouring HAART in patients with haemophilia, who were the primary population of interest in this review. However, this finding was based on only two studies, and there were too few data to provide an accurate effect estimate and to determine if the effect differed from that in other populations. There were too few studies to explore the effects of other variables (such as age, liver-disease severity, CD4 count, ARV regimen, alcohol abuse, and time since HCV infection), using appropriate statistical methods.

4.4 Generalisability of the findings

Most studies included in this review were conducted in Europe; none were from the UK. Potential differences in the management of HIV/HCV co-infection across different health systems may limit the applicability of the review findings to co-infected populations in the UK. Most participants included in the studies were under 50 years old. The burden of other co-morbidities is likely to be higher in an older population. This, in addition to the toxicity of other treatments, may impact differently upon liver disease. This limits the applicability of the results to older populations, especially given the increasing life expectancy of people with HIV and HCV, and the growing proportion of people with HIV aged 50 years or older. The applicability of the findings to Black and minority ethnic groups affected by different strains of HIV, who are likely to have been under-represented in the included cohorts, is also unclear, although results from the two studies that included mostly Black participants (Limketkai et al. 2012; Mehta et al. 2005) were consistent with those of other included cohorts.

Two studies included a substantial proportion of patients with haemophilia (Qurishi et al. 2003; Ragni et al. 2009), so these studies are of greater relevance for this review. All other studies either mostly included patients with a history of injection drug use, or did not report on their drug use or likely mode of infection. Participants with a history of injection drug use are likely to differ in significant ways from patients with haemophilia. For instance, co-infected patients with haemophilia are more likely to have contracted HCV and HIV through repeated exposure to infected blood products from early childhood, whereas injection drug users may be more likely to have been infected in adolescence or adulthood. For this reason, liver damage and progression to AIDS may have occurred from a younger age in patients with haemophilia. It is also possible that comorbidities and

interactions with therapies specific to patients with haemophilia may affect liver-disease outcomes. Although the results of studies of patients with haemophilia did not differ significantly from those of other populations, the unique circumstances of patients with haemophilia should be considered when interpreting the results from populations without haemophilia.

4.5 Conclusions

The use of HAART is associated with a significantly reduced liver-related mortality in patients co-infected with HIV and HCV. Evidence of a positive association between HAART and/or ARV monotherapy with liver-disease progression is less clear, although there is no evidence to suggest that the absence of antiretroviral therapy is preferable.

4.5.1 Implications for policy and clinical practice

The findings of this review support the use of HAART in patients co-infected with HIV and HCV as recommended in the EACS and BHIVA guidelines (Brook et al. 2010; Rockstroh et al. 2008). However, given the increased risk of liver-related morbidity in patients co-infected with HIV and HCV and the limited evidence on the impact of HAART and liver disease progression, the need for monitoring liver-disease progression in this population clearly remains. Future management of co-infected patients is likely to evolve with the advent of new directly acting antivirals (DAAs), and several are currently being reviewed by NICE (2014a, b; 2015a, b).

4.5.2 Further research

Few included studies reported data separately for different antiretroviral classes and combinations. Several studies comparing different regimens did not compare HAART with untreated people and were therefore excluded from our review. Given the common use of HAART in HIV management, a systematic review on the acute and chronic effects of different HAART regimens would be useful. In addition, the mechanisms by which liver-disease mortality is reduced with HAART are still largely unknown (Ragni et al. 2009). It may be that the effects of HAART on liver-disease progression and mortality occur through immune reconstitution, viral suppression or a combination of both (Kramer et al. 2007), but further research in this area is required.

Once further data on the impact of HAART on liver-disease progression in co-infected patients are available, an update of this systematic review may be appropriate. Further research on the impact of HAART on liver-disease outcomes in specific populations (such as patients with haemophilia) would also help to clarify the applicability of the review findings to different subgroups.

There is little long term evidence on the impact of HAART on health-related quality of life in HIV/HCV co-infected patients (Jin et al. 2014), and exploring qualitative evidence on patient experience and perception of HAART/ARV monotherapy in this population was beyond the scope of this review. A systematic review of qualitative studies on patient perspectives (and possibly further primary qualitative studies) may help to provide a more complete picture of the evidence on the effect of HAART/ARV monotherapy in patients co-infected with HIV and HCV.

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Appendices

Appendix 1: Authorship

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Mark Simmonds: Contributed to the protocol development. Performed the statistical analyses and drafted the analysis results, performed full-text study selection, data extraction and quality assessment; contributed generally to the writing of the report.

Ginny Brunton: Contributed to the protocol development and provided comments on drafts of the report.

Amanda Sowden: Contributed to the protocol development. Took overall managerial responsibility for the project, contributed to all aspects of the project, and provided comments on drafts of the report.

Acknowledgements

The authors would like to thank members of our advisory group, including Joseph Peaty and Mark Ward from Tainted Blood for providing testimonies on living with HIV, Hepatitis C and haemophilia and on undergoing antiretroviral therapy, for suggesting references for inclusion, and for commenting on the draft report. We thank Professor Will Irving, Professor of Virology, Queen's Medical Centre, Nottingham, for his assistance and advice in the interpretation of the studies and for commenting on the draft report. We also thank Professor James Thomas, Professor of Social Research and Policy, UCL Institute of Education, University College London, for his advice and support.

Funding

This is an independent report commissioned and funded by the Policy Research Programme in the UK Department of Health. The views expressed are not necessarily those of the Department.

Conflicts of interest

There were no conflicts of interest in the writing of this report.

Contributions

The opinions expressed in this publication are not necessarily those of the University of York, the EPPI-Centre or the funders. Responsibility for the views expressed remains solely with the authors.

Appendix 2: Search strategy

Medline

Searched 18/06/14 via OVID interface.

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

No date or language limits applied.

Search strategy:

- 1 exp HIV/ (84307)
- 2 exp HIV Infections/ (233038)
- 3 exp Hepatitis C/ (47865)
- 4 exp Hepacivirus/ (24124)
- 5 (1 or 2) and (3 or 4) (7098)
- 6 exp Antiretroviral Therapy, Highly Active/ (17442)
- 7 Anti-Retroviral Agents/ (5840)
- 8 Antiviral Agents/ (56460)
- 9 Anti-HIV Agents/ (34699)
- 10 6 or 7 or 8 or 9 (106310)
- 11 5 and 10 (2269)
- 12 exp Fibrosis/ (50801)
- 13 Liver Cirrhosis/ (56237)
- 14 Liver Diseases/ (58223)
- 15 Liver/ (373600)
- 16 Drug-Induced Liver Injury/ (23066)
- 17 (liver adj2 (fibrosis or cirrhosis)).ti,ab. (29669)
- 18 12 or 13 or 14 or 15 or 16 or 17 (530439)
- 19 11 and 18 (559)

Embase

Searched 18/06/14 via OVID interface.

Database: Embase <1974 to 2014 June 17>

No date or language limits applied.

Search strategy:

- 1 exp Human immunodeficiency virus/ (133543)
- 2 exp Human immunodeficiency virus infection/ (298276)
- 3 exp hepatitis C/ (73811)
- 4 exp Hepatitis C virus/ (43388)
- 5 (1 or 2) and (3 or 4) (16222)
- 6 exp highly active antiretroviral therapy/ (29310)
- 7 antiretrovirus agent/ (33456)
- 8 antiviral agent/ (53721)
- 9 anti human immunodeficiency virus agent/ (13395)
- 10 6 or 7 or 8 or 9 (113132)
- 11 5 and 10 (4430)
- 12 exp fibrosis/ (153092)
- 13 liver cirrhosis/ (94465)
- 14 liver disease/ (83604)
- 15 liver/ (400588)
- 16 toxic hepatitis/ (8742)
- 17 liver injury/ or liver toxicity/ (92069)
- 18 (liver adj2 (fibrosis or cirrhosis)).ti,ab. (41464)
- 19 12 or 13 or 14 or 15 or 16 or 17 or 18 (738045)

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20 11 and 19 (1573)

21 limit 20 to Embase (1496)

Appendix Table 1: Results from bibliographic searches

	Results	After deduplication
MEDLINE	559	522
EMBASE	1,496	1,226
Total	2,055	1,748

Appendix 3: Quality assessment and risk of bias

Risk of bias was evaluated using a modified version of the Newcastle-Ottawa quality assessment tool (Wells et al. [2014]). Following this tool, three main domains were considered: participant selection, confounding and outcomes. However, two main modifications were made for the purposes of this review. First, questions were devised to inform a judgement about risk of bias for each of these three domains within each study, whereas the Newcastle-Ottawa tool is designed to provide an overall quality score for each study. We felt that the use of quality scores was potentially misleading. For instance, a study with high risk of confounding due to lack of adjustment in its analysis may still receive a relatively high quality score if it meets all other criteria. Secondly, the relevance of the study participants to the key population of interest for this review was considered, whereas the Newcastle-Ottawa tool does not address this question.

Appendix Table 2: Quality assessment criteria

Participant selection	
Question 1	Was the sample representative of study population of interest? (Yes/No/Unclear)
Question 2	Was there no presence of outcome at baseline? (Yes/No/Unclear)
Question 3	Was HCV assessed using valid methods (e.g. polymerase chain reaction)? (Yes/No/Unclear)
Risk of selection bias	Risk of bias associated with participant selection (High/Low/Unclear)
Confounding	
Question 4	Group differences: Were there significant differences in population characteristics between intervention and comparison groups? (Yes/No/Unclear)
Question 5	Was there adjustment for relevant confounders in the analyses? (e.g. age, sex/gender, duration of HCV infection, alcohol abuse, HCV treatment, baseline liver damage) (Yes/No/Unclear)
Question 6	Was risk of cross-over addressed? (i.e. risk that comparison group received HAART/ARV monotherapy during the study) (Yes/No/Partly)
Risk of confounding bias	Risk of bias associated with confounding (High/Low/Unclear/Moderate)
Outcome measurement	
Question 7	Was the outcome assessed using valid methods? (e.g. using hospital registry data) (Yes/No/Unclear)
Question 8	Was follow-up duration adequate/was follow-up sufficient to assess the impact of the intervention on the outcome of interest? (report assessment separately if the answer differs per outcome) (Yes/No/Unclear)
Question 9	Was loss to follow-up acceptable? (Yes/No/Unclear/Not applicable)
Risk of outcome measurement bias	Risk of bias associated with outcome measurement (High/Low/Unclear)

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Relevance	
Relevance to the review	Were there any concerns about the relevance of this study in the context of the review? (e.g. low proportion of patients with haemophilia) (High/Moderate/Low relevance)

Appendix Table 3: Quality assessment and risk of bias results

Study	Sample	Baseline	Confounding	Outcome assessment	Follow-up	Relevance
Bruno (2007)	<p>Representative: Yes. All eligible patients in a medical centre</p> <p>Selection bias: Low</p> <p>Differences between groups: Unclear</p>	<p>Outcome at baseline: No</p> <p>HIV/HCV assessed appropriately? Yes. HCV RNA</p>	<p>Adjustment for relevant confounders? Unclear. May not be adjusted analyses</p> <p>Cross-over risk addressed? Partly. HAART only recorded from 1st event of decompensation</p> <p>Confounding bias: Moderate. Insufficient information on methods of adjustment used. Unclear how participants were assigned to groups</p>	<p>Outcome assessed using valid methods? Yes</p> <p>Outcome measurement bias: Low</p>	<p>Adequate follow-up duration? Yes</p> <p>Limited loss to follow-up? NA. Only participants with follow-up data were included</p>	Unclear. Mode of infection unknown
Giron-Gonzalez (2007)	<p>Representative: Unclear if consecutive</p> <p>Selection bias: Unclear if consecutive</p> <p>Differences between groups: Yes. Higher decompensation frequency before baseline in untreated group ($p=0.006$). No</p>	<p>Outcome at baseline: No. Stable and compensated cirrhosis. Patients with previous decompensation analysed separately</p> <p>HIV/HCV</p>	<p>Adjustment for relevant confounders? Yes</p> <p>Child-Pugh index and MELD score (decompensation outcome); Plasma HCV viral load; Child-Pugh index ≥ 9; Child-Pugh index progression; MELD score ≥ 14, previous or occurring decompensation at follow-up; >1 decompensation at follow-up (mortality outcome). Other</p>	<p>Outcome assessed using valid methods? Yes</p> <p>Outcome measurement bias: Low</p>	<p>Adequate follow-up duration? Yes</p> <p>Limited loss to follow-up? Yes</p>	Low. 90% IDUs

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Study	Sample	Baseline	Confounding	Outcome assessment	Follow-up	Relevance
	significant differences in alcohol abuse, IDU and CD4 count.	assessed appropriately? No. HCV antibodies only	variables measured at baseline not adjusted for because not independently associated with outcomes Cross-over risk addressed? Partly. No. HAART= <80% adherence. Some patients in the comparison group were exposed to HAART Confounding bias: Moderate. Some patients in comparison group were exposed to HAART			
Limketkai (2012)	Representative: Unclear. 80% Black (unclear what population was aimed for) Selection bias: Low Differences between groups: Unclear	Outcome at baseline: Yes 11% at baseline with F4 Fibrosis stage HIV/HCV assessed appropriately? Yes	Adjustment for relevant confounders? Yes. Adjusted for age, sex, race, IDU, time-varying CD4 cell count and current HAART exposure. Cross-over risk addressed? Yes. HAART exposure addressed as a time-varying measure; current HAART exposure adjusted for in analyses. Confounding bias: Low. Adjusted for age, sex, race,	Outcome assessed using valid methods? Yes Outcome measurement bias: Low	Adequate follow-up duration? Yes. Median 5.82 years Limited loss to follow-up? Unclear. NR	Low. 66% men

Study	Sample	Baseline	Confounding	Outcome assessment	Follow-up	Relevance
			injection drug use, time-varying CD4 cell count and current HAART exposure.			
Macías (2006)	<p>Representative: Yes. >1 liver biopsy. May be different from other co-infected patients</p> <p>Selection bias: Low</p> <p>Differences between groups: Unclear</p>	<p>Outcome at baseline: No HIV/HCV assessed appropriately? Yes. HCV RNA</p>	<p>Adjustment for relevant confounders? Yes. Age, undetectable HIV viraemia, genotype 3, baseline ALT, baseline necroinflammatory activity, time between liver biopsies, HCV treatment response</p> <p>Cross-over risk addressed? Partly. Only at follow-up</p> <p>Confounding bias: Moderate adjustment for relevant confounders, but risk of cross-over unclear</p>	<p>Outcome assessed using valid methods? Yes. Liver biopsy</p> <p>Outcome measurement bias: Low</p>	<p>Adequate follow-up duration? Yes. Spanned over 22 years</p> <p>Limited loss to follow-up? NA Only participants with follow-up data were included</p>	Low. Primarily IDUs
Macías (2009)	<p>Representative: Yes</p> <p>Selection bias: Low</p> <p>Differences between groups: Unclear. NR</p>	<p>Outcome at baseline: No HIV/HCV assessed appropriately? Yes. HCV RNA</p>	<p>Adjustment for relevant confounders? Yes. Age, undetectable HIV viraemia, genotype 3, baseline ALT, baseline necroinflammatory activity, time between liver</p>	<p>Outcome assessed using valid methods? Yes. Biopsy</p> <p>Outcome measurement</p>	<p>Adequate follow-up duration? Yes</p> <p>Limited loss to follow-</p>	Low. 90% IDUs

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Study	Sample	Baseline	Confounding	Outcome assessment	Follow-up	Relevance
			<p>biopsies, HCV treatment response</p> <p>Cross-over risk addressed? Partly. Comparator included ARV monotherapy and untreated</p> <p>Confounding bias: Low. Multivariate adjusted model used</p>	<p>bias: Unclear. Selective reporting? Only two AOR reported, out of nine subgroup analyses</p>	<p>up? NA. Only participants with follow-up data were included</p>	
Mariné-Barjoan (2004)	<p>Representative: Yes. Appears to be all eligible; reasonable inclusion criteria</p> <p>Selection bias: Low</p> <p>Differences between groups: Unclear</p>	<p>Outcome at baseline: No HIV/HCV assessed appropriately? Yes. HCV RNA</p>	<p>Adjustment for relevant confounders? No</p> <p>Cross-over risk addressed? Partly. Exposure only measured at time of biopsy</p> <p>Confounding bias: High. No adjustments for relevant confounders</p>	<p>Outcome assessed using valid methods? Yes. Liver biopsy</p> <p>Outcome measurement bias: Low</p>	<p>Adequate follow-up duration? Yes. Median duration of HCV infection 15 years</p> <p>Limited loss to follow-up? NA. Only participants with follow-up data were</p>	<p>Low. 72% IDU, 4% contracted through blood transfusion</p>

Study	Sample	Baseline	Confounding	Outcome assessment	Follow-up	Relevance
					included	
Mehta (2005)	<p>Representative: Unclear. Partly random cohort, partly not. Unclear if consecutive</p> <p>Selection bias: Unclear</p> <p>Differences between groups: Unclear. Though most no-HAART appeared to come from the clinical care cohort, which was less likely to have abused alcohol and had higher ALT levels at biopsy</p>	<p>Outcome at baseline: Unclear. Liver disease reported at one point only</p> <p>HIV/HCV assessed appropriately? Yes. HCV RNA</p>	<p>Adjustment for relevant confounders? No. Multivariate models used, but not reported for HAART exposure</p> <p>Cross-over risk addressed? Partly. Only about half of the comparison group were completely naive to HAART.</p> <p>Confounding bias: High. No adjustments</p>	<p>Outcome assessed using valid methods? Yes. Authors stated that METAVIR scores (fibrosis+necro-inflammatory activity) were not analysed, because all patients with MHA1 F3 or above also had a METAVIR score of 2 or higher</p> <p>Outcome measurement bias: High</p>	<p>Adequate follow-up duration? No</p> <p>Limited loss to follow-up? Unclear. Minimum 2 years HAART prior to liver biopsy (no range reported). 2 years may not be sufficient, depending on baseline liver damage severity</p>	Low. Large proportion of IDUs
Merchante (2006)	<p>Representative: Unclear. Insufficient</p>	<p>Outcome at baseline: No</p>	<p>Adjustment for relevant confounders? No. Only raw data</p>	<p>Outcome assessed using</p>	<p>Adequate follow-up</p>	Low. Mostly current/

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Study	Sample	Baseline	Confounding	Outcome assessment	Follow-up	Relevance
	<p>information</p> <p>Selection bias: Unclear. Insufficient information on selection</p> <p>Differences between groups: Unclear. NR</p>	<p>HIV/HCV assessed appropriately? Yes. HCV RNA</p>	<p>reported for outcome of interest</p> <p>Cross-over risk addressed? No. 58% with prior HAART history, unclear if all were in intervention group</p> <p>Confounding bias: High. Unadjusted data and unclear risk of cross-over</p>	<p>valid methods? Yes. Registry data, definition provided</p> <p>Outcome measurement bias: Low</p>	<p>duration? Yes. Up to 70 months</p> <p>Limited loss to follow-up? Unclear. NR</p>	<p>previous IDUs</p>
Pineda (2009)	<p>Representative: Yes. Clear selection criteria</p> <p>Selection bias: Low</p> <p>Differences between groups: Unclear. Comparison group very small</p>	<p>Outcome at baseline: No. Stated as an exclusion criterion</p> <p>HIV/HCV assessed appropriately? Yes. HCV RNA</p>	<p>Adjustment for relevant confounders? No. Not for decompensation. Unclear for liver-related mortality (variables unclear)</p> <p>Cross-over risk addressed? Partly. Mixed intervention group (some with HAART history at baseline). History of comparison group unknown. Criteria for exposure/non-exposure unreported.</p> <p>Confounding bias: High. Especially for unadjusted decompensation results</p>	<p>Outcome assessed using valid methods? Yes. Definition provided</p> <p>Outcome measurement bias: Low</p>	<p>Adequate follow-up duration? Yes</p> <p>Limited loss to follow-up? Yes</p>	<p>Low. 86% IDU history</p>

Study	Sample	Baseline	Confounding	Outcome assessment	Follow-up	Relevance
Qurishi (2003)	<p>Representative: Unclear. Unclear if consecutive</p> <p>Selection bias: Unclear</p> <p>Differences between groups: Yes. Statistically significant higher bilirubin and glutamyl-transpeptidase levels for HAART vs untreated; statistically significant higher glutamyl-transpeptidase for HAART vs untreated. No statistically significant differences in demography, haemophilia, substance abuse, HBV and HIV viral load at baseline</p>	<p>Outcome at baseline: No HIV/HCV assessed appropriately? Yes. HCV RNA</p>	<p>Adjustment for relevant confounders? Yes. Sex, age, risk category, alcohol misuse, HBV, CD4 count, AAT, AST, GGT, cholinesterase, bilirubin, platelets count, immunoglobulin concentration. No adjustment for viral loads (not available before 1996). Fixed and time-dependent covariates addressed separately. Risk of over-adjustment due to correlations between covariates?</p> <p>Cross-over risk addressed? Yes. Comparison group was untreated throughout. HAART and ARV monotherapy clearly defined</p> <p>Confounding bias: Low. Probably not</p>	<p>Outcome assessed using valid methods? Yes. Definition provided, assessor blinded to exposure</p> <p>Outcome measurement bias: Low. Assessor blinded to exposure</p>	<p>Adequate follow-up duration? Yes. Beyond 12 years</p> <p>Limited loss to follow-up? Yes. Approx. 23% appear to have been lost at 5 years</p>	<p>High. 81% with haemophilia, 94% men</p>
Ragni (2009)	<p>Representative: Yes. All eligible patients</p>	<p>Outcome at baseline: No HIV/HCV</p>	<p>Adjustment for relevant confounders? No. Cox model was adjusted, but</p>	<p>Outcome assessed using valid methods?</p>	<p>Adequate follow-up duration?</p>	<p>High. 100% men with</p>

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Study	Sample	Baseline	Confounding	Outcome assessment	Follow-up	Relevance
	<p>included</p> <p>Selection bias: Low</p> <p>Differences between groups: Yes. Mean age at HIV seroconversion: significantly older in untreated group (35.7), compared with HAART group (20.8) and ARV monotherapy (26.6), $p=0.03$. HAART group significantly older than ARV monotherapy and untreated combined ($p=0.05$). CD4 count significantly lower in HAART group, followed by untreated and then ARV monotherapy ($p<0.01$). HBV (HBsAg+) significantly higher in untreated and ARV monotherapy vs HAART ($p=0.002$). Mean age at ESLD older in untreated (53.0), followed by</p>	<p>assessed appropriately? No. HCV RNA NR. 100% HCV positive; active HCV unclear</p>	<p>incidence of ESLD not adjusted</p> <p>Cross-over risk addressed? Yes. All HAART group had previously received ARV monotherapy. Untreated group received no treatment, with reasons provided</p> <p>Confounding bias: Low (high for unadjusted results, with several important between-group differences)</p>	<p>Unclear. ESLD definition not reported</p> <p>Outcome measurement bias: Unclear. ESLD not reported</p>	<p>Yes. 35 years</p> <p>Limited loss to follow-up? Unclear. NR</p>	<p>haemophilia</p>

Study	Sample	Baseline	Confounding	Outcome assessment	Follow-up	Relevance
	HAART (43.4) and ARV monotherapy (34.5) (p-value NR)					
Reiberger (2010)	<p>Representative: Unclear. Unclear if consecutive, limited reporting on sampling</p> <p>Selection bias: High. 19% with fibrosis stage 4 at baseline. Reporting of selection limited</p> <p>Differences between groups: Unclear. NR. Unclear how patients were assigned to groups</p>	<p>Outcome at baseline: Yes. 19% with fibrosis stage 4</p> <p>HIV/HCV assessed appropriately? Yes. HCV RNA</p>	<p>Adjustment for relevant confounders? No. No adjustments</p> <p>Cross-over risk addressed? No. Unclear when exposure was measured</p> <p>Confounding bias: High. No adjustment and risk of cross-over unclear</p>	<p>Outcome assessed using valid methods? Yes. Liver biopsy. Assessors blinded to clinical history</p> <p>Outcome measurement bias: Low</p>	<p>Adequate follow-up duration? Unclear. NR</p> <p>Limited loss to follow-up? NA. Only participants with follow-up data were included</p>	Low. Mostly IDUs
Schiavini (2006)	<p>Representative: Yes. Appears to be all patients in stated time frame</p> <p>Selection bias: Unclear</p> <p>Differences between groups: Unclear. NR</p>	<p>Outcome at baseline: Unclear. Some patients may have had the highest possible Ishak Knodell stage</p>	<p>Adjustment for relevant confounders? No. No adjustments for HAART</p> <p>Cross-over risk addressed? Partly. Reported absence of ARV therapy, though definition NR</p> <p>Confounding bias: High.</p>	<p>Outcome assessed using valid methods? Yes. Liver biopsy</p> <p>Outcome measurement</p>	<p>Adequate follow-up duration? Yes. 4.5 years</p> <p>Limited loss to follow-up? NA.</p>	Unclear. Mode of infection NR

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Study	Sample	Baseline	Confounding	Outcome assessment	Follow-up	Relevance
		HIV/HCV assessed appropriately? Yes. HCV RNA	Unadjusted values only	bias: Low	Only participants with follow-up data were included	

NA: Not applicable; NR: Not reported; AOR: Adjusted odds ratio; ALT: alanine aminotransferase; IDU: Injection drug use

Appendix 4: Characteristics of included studies

Appendix Table 4: Study characteristics

Author (year)	Country	Industry funding	Prospective/retrospective?	Inclusion criteria	Exclusion criteria	Start date	End date	Total N	Intervention N	Comparator N
Bruno (2007)	Italy	No	Retrospective	>18 years; HCV or HBV Cirrhosis (compensated) Elevated alphafetoprotein levels (0.200 ng/mL)	HCC	1999	2004	53	29	24
Giron-Gonzalez (2007)	Spain	No	Prospective	Anti-HCV antibodies; cirrhosis; previous decompensation eligible if stable and compensated at baseline	liver cancer; HBV+	2004	Oct 2006	92	73	19
Limketkai (2012)	USA	No	Prospective	HIV/HCV co-infection; liver biopsy between 1993 and 2011	NR	1993	2011	638	440 (69%)	198 (31%)
Macías (2006)	Spain	No	Retrospective self-described cross-sectional but treated as retrospective cohort because there were attempts to assess progression	HIV/HCV who underwent liver biopsy	HCV treatment before biopsy; HBV+ and other possible liver disease causes (incl. tumour)	1991	2005	683	509	174

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Author (year)	Country	Industry funding	Prospective/retrospective?	Inclusion criteria	Exclusion criteria	Start date	End date	Total N	Intervention N	Comparator N
			between two time points							
Macías (2009)	Spain	No	Retrospective	HCV (RNA); >1 liver biopsy, separated by at least 1 year	Other concomitant causes of liver disease	1986	2008	135	113 (110 HAART, 3 ARV monotherapy)	22 (analysis suggests 26, table 4)
Mariné-Barjoan (2004)	France	No	Retrospective Self-described as case-control but classed as cohort because it attempts to capture disease progression based on two separate time points	HCV RNA; liver biopsy before July 2000	HCV treatment; HBsAg+	1997	2000	116 (co-infected subgroup)	91	25
Mehta (2005)	USA	No	Prospective	Co-infected patients with at least 2 years of HAART; HCV treatment naive	ESLD; lost to follow-up (5)	2001	NR (median f-u 5 years (IQR 2.9-7.5))	210	135	75

Author (year)	Country	Industry funding	Prospective/retrospective?	Inclusion criteria	Exclusion criteria	Start date	End date	Total N	Intervention N	Comparator N
Merchante (2006)	Spain	Yes (Glaxo-SmithKline)	Prospective	HIV-HCV presenting with 1st decompensation	Metabolic or autoimmune liver disease; <18yrs; previous decompensation	1997	2004(?)	153	101	52
Pineda (2009)	Spain	No	Prospective	HCV; Child-Pugh-Turcotte (CPT) class A cirrhosis; no decompensation of liver disease	Decompensation at baseline	1996	2006	154	145	9
Qurishi (2003)	Germany	No	Retrospective	Co-infected patients regularly treated at hospital department	NR	1990	2002	285	HAART: 93; ARV monotherapy: 55	137
Ragni (2009)	USA	No	Prospective	HCV positive since 1978, with or without HIV	NR	1970	2005	85 (HIV subgroup)	HAART: 20; ARV monotherapy: 40	25
Reiberger (2010)	Austria	No	Retrospective	HIV-HCV co-infected patients with available data on portal pressure and liver histology	HCV therapy history; HBsAg+; AIDS-defining condition; TB history	NR	NR	74	49	25

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Author (year)	Country	Industry funding	Prospective/retrospective?	Inclusion criteria	Exclusion criteria	Start date	End date	Total N	Intervention N	Comparator N
Schiavini (2006)	Italy	NR	Retrospective	HIV-HCV co-infection; liver biopsy specimen	NR	1985	NR (last recruited January 2002, median f-u 4.5 years)	36 (subgroup with paired liver biopsies)	20	16

ESLD: end-stage liver disease; NR: not reported; f-u: follow-up; IQR: interquartile range

Appendix Table 5: Treatment regimens and concomitant treatment

Author (year)	ARV monotherapy, HAART or both	ARV monotherapy regimens	HAART regimens	“No antiretroviral therapy” group inclusion criteria	Concomitant treatment
Bruno (2007)	HAART only	NA	After 1st event of decompensation	No HAART after 1st event of decompensation	HCV treatment unknown. None for 33% with genotype 3
Giron-Gonzalez (2007)	HAART only	NA	2 NNRTIs +PI (51%) or +efavirenz (34%) or +abacavir. No nevirapine	Absence of HAART = <80% adherence during follow-up (definition from related study), rather than permanent discontinuation	8% (of total)
Limketkai (2012)	HAART and/or ARV monotherapy	NA	Including multiple agents with at least 1 PI, NNRTI or	No HAART/ARV monotherapy at time of	NR

Author (year)	ARV monotherapy, HAART or both	ARV monotherapy regimens	HAART regimens	“No antiretroviral therapy” group inclusion criteria	Concomitant treatment
			integrase inhibitor	liver biopsy	
Macías (2006)	HAART or ARV monotherapy	Nucleoside analogue or dual therapy (merged with comparator group)	Based on PI; nevirapine; efavirenz; PI switched to nevirapine; PI switched to efavirenz; backbone nucleoside analogues; others. Nucleoside analogues and PI most frequent. Median exposure from 87 to 364 weeks depending on regimens.	Mixed drug naive (67%) and ARV monotherapy (33%)	No HCV therapy
Macías (2009)	HAART and/or ARV monotherapy	NR (3 patients at f-u)	At f-u. Only PI-based (43); only nevirapine based (14), only efavirenz based (20); other (33)	Lack of antiretroviral therapy	44% HCV treatment (across groups)
Mariné-Barjoan (2004)	HAART only	NA	At time of biopsy. Non-nucleoside analogue (28 patients), nucleoside analogue (89), PI (72) (some patients received more than one class).	At time of biopsy	no HCV therapy
Mehta (2005)	HAART and/or ARV monotherapy	NRTIs only, PI/NNRTI +NRTIs	Cumulative HAART exposure	none at biopsy (of which about half were totally naive)	NR

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Author (year)	ARV monotherapy, HAART or both	ARV monotherapy regimens	HAART regimens	“No antiretroviral therapy” group inclusion criteria	Concomitant treatment
Merchante (2006)	HAART only	NA	Received during follow-up. Nucleoside analogues: 100%; PIs: 70%; non-nucleoside analogues: 43%; 42% stavudine+lamivudine	No HAART during follow-up	NR
Pineda (2009)	HAART only	NA	72 (50% of intervention) received PI throughout f-u. 36 (25%) NNRTI combinations. 29 switched (from PI to NNRTI or vice versa) during f-u.	No HAART from baseline to follow-up	43% of total population HCV therapy at follow-up
Qurishi (2003)	HAART and/or ARV monotherapy	Nucleoside analogues only (35% monotherapy). Transient interruption in 7%. Available from 1992	PI (76%) or NNRTI (24%) based. Transient interruption in 6%. Available from 1995	Did not receive any HAART/ARV monotherapy	No HCV treatment
Ragni (2009)	HAART and/or ARV monotherapy	NR	HAART: protease inhibitor (95%), NNRTI (5%). All had previously received HAART/ARV monotherapy	Unwilling or died before drugs were available	7 patients had liver biopsies pre-transplant or pre-HCV treatment (group NR)
Reiberger (2010)	HAART only	NA	NR. Unclear when exposure was measured	NR	No HCV treatment

Author (year)	ARV monotherapy, HAART or both	ARV monotherapy regimens	HAART regimens	“No antiretroviral therapy” group inclusion criteria	Concomitant treatment
Schiavini (2006)	HAART and/or ARV monotherapy	Single or dual drug therapy	0	Absence of antiretroviral therapy	Interferon 92% across groups (of which 6% has SVR)

NA: not applicable; NR: not reported; f-u: follow-up; SVR: systemic vascular resistance

Appendix Table 6: Overlap across Spanish cohort studies

Study	Source	N	Key patient characteristics	Outcome	Notes
Giron-Gonzalez (2007)	3 hospitals in southern Spain	92	Cirrhosis (compensated and decompensated)	Decompensation (subgroup), Liver related mortality	Possible overlap with Pineda (2009) and Merchante (2006).
Macías (2006)	10 tertiary care centres from southern Spain and Madrid	683	All fibrosis stages	Advanced Fibrosis and Fibrosis progression rate (FPR: ratio between liver damage at f-u and estimated duration of HCV infection)	Possible partial overlap with Macías (2009)
Macías (2009)	16 centres, 9 hospitals	135 (with paired liver biopsies)	No cirrhosis	Fibrosis progression	Paired biopsies subgroup
Merchante (2006) ⁸	4 southern Spain hospitals	153	Decompensated cirrhosis (no previous decompensation)	Liver mortality	Probable overlap with Giron-Gonzalez (2007) but separate from Pineda
Pineda (2009) ⁹	7 southern Spain hospitals	154	Cirrhosis class A, no decompensation	Decompensation; Liver mortality	Possible overlap with Giron-Gonzalez (2007) but separate from Merchante

Appendix 5: Detailed results of studies on liver-related mortality

Appendix Table 7: Liver-related mortality study results

Study	Intervention	Outcome	Follow-up duration	Effect estimate	Adjustments	Included in meta-analysis?
Bruno (2007)	HAART	Liver-related mortality	1 year	RR 0.51 (95% CI 0.30 to 0.85)	None	Yes
Bruno (2007)	HAART	Liver-related mortality	3 years	RR 0.73 (95% CI 0.58 to 0.91)	None	No ¹
Giron-Gonzalez (2007)	HAART	Liver-related mortality	Median 20 months (IQR 12-28)	HR 0.35 (95% CI 0.23 to 0.53)	HCV viral load, liver disease severity, liver disease progression, decompensation during or before follow-up	Yes
				RR 0.22 (95% CI 0.11 to 0.42)	None	Yes
Limketkai (2012)	HAART (mostly) and ARV monotherapy	Liver-related mortality, end stage liver disease and hepatocellular carcinoma ²	Median 5.82 years (IQR 3.42-8.85)	RR 0.34 (95% CI 0.27 to 0.43)	Age, sex, race, injection drug use, time-varying CD4 cell count and current HAART exposure	Yes
				RR 0.46 (95% CI 0.35 to 0.61)	None	Yes
Merchante (2006)	HAART	Liver-related mortality	Up to at least 5.8 years	HR 0.5 (95% CI 0.3 to 0.9) ²	None	No
Pineda (2009)	HAART	Liver-related mortality	Mean 36 months,	HR 0.88 (95% CI 0.48	Yes (covariates NR)	No

Study	Intervention	Outcome	Follow-up duration	Effect estimate	Adjustments	Included in meta-analysis?
			range 1 to 131 months	to 1.61)		
				RR 0.62 (95% CI 0.09 to 4.33)	None	Yes
Qurishi (2003)	HAART	Liver-related mortality	12 years	OR 0.11 (95% CI 0.08 to 0.14)	Sex, age, risk category, alcohol misuse, HBV, CD4 count, AAT, AST, cholinesterase bilirubin, platelets count, immunoglobulin	Yes
				RR 0.16 (95% CI 0.04 to 0.69)	None	Yes
Qurishi (2003)	ARV monotherapy	Liver-related mortality	12 years	OR 0.031 (95% CI 0.006 to 0.151)	Sex, age, risk category, alcohol misuse, HBV, CD4 count, AAT, AST, bilirubin, platelets count, immunoglobulin concentration	No
Ragni (2009)	HAART	Liver-related mortality	Up to 35 years	RR 0.50 (95% CI 0.11 to 2.31)	None	Yes
Ragni (2009)	ARV monotherapy	Liver-related mortality	Up to 35 years	RR 0.75 (95% CI 0.26 to 2.20)	None	No

¹ One year follow-up was preferred for the meta-analysis because there were no survivors at three years in the control group. Once there are no survivors left, the relative risk becomes increasingly biased towards unity, because HAART group people continue to die but control group do not.

² The number of liver-related mortality events per group was unclear, although at least 63% of events were liver-related mortality.

Appendix 6: Studies included in Kramer et al. (2007)

Appendix Table 8: Selection decision for studies included in the Kramer et al. (2007) review

Study	Decision
Benhamou (2001)	Exclude- comparator (comparing different regimens)
De Bona (2003)	Exclude- design (cross-sectional study)
Fuster (2004)	Exclude- design (cross-sectional study)
Macías (2004)	Exclude- comparator (not comparing HAART vs no treatment)
Mariné-Barjoan (2004)	Include
Martin-Carbonero (2004)	Exclude- design (cross-sectional study)
Mehta (2005)	Include
Qurishi (2003)	Include
Sterling (2004)	Exclude- design (cross-sectional study)
Tural (2003)	Exclude- design (cross-sectional study)
Vento (1998)	Exclude- comparator (not comparing HAART vs no treatment)

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First produced in 2015 by:

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ISBN: 978-1-907345-80-7

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