# Coinfection by HIV and hepatitis A, B and C virus in adult patients. Review and GESIDA/PNS recommendations


## Working group for the elaboration of recommendations on viral hepatitis in HIV-infected patients

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## Introduction

There is a growing body of evidence about the relevance of viral hepatitis in the frame of HIV/AIDS epidemics in Spain, and those due to hepatitis C virus (HCV) are especially noteworthy. This epidemiologic situation has an increasing clinical importance, mainly because current antiretroviral therapies have a favourable impact on the morbility and mortality caused by HIV infection and its associated pathologies. As a result, there is a continued debate on the benefits and strategies of anti-viral treatments against hepatotropic viruses including the chance of liver transplantation in selected cases.

From this background, the Secretary of the National Plan on AIDS (SPNS) and the AIDS Study Group (GESIDA) of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC), on the basis of elaborating documents with recommendations about fundamental aspects for the management of HIV infection, have set up a working group with the participation health professionals from SPNS, GESIDA, and the Spanish Association for the Study of the Liver (AEHH) as well as the Quality Control Programme of the SEIMC, together with other experts. The goal of the Working Group is to release updated reports reviewing key topics of the coinfections by hepatotropic viruses and HIV, regarding epidemiology, diagnosis, prevention and treatment so that recommendations for the clinical management of these patients can be established.

These reports, as well as other reports edited by SPNS and GESIDA altogether, intend to have two main utilities. First, to assist healthcare and public health professionals on decision making. Second, to provide health authorities from different public institutions at the Autonomous Communities (CCAA) and the very Ministry of Health with a reference

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tool to plan health strategies. The work of elaborating clinical and preventive recommendations is well-established within the activities of GESIDA and SPNS, and it is highlighted by the National Commission and included in the Plan of Multisectorial Mobilization against HIV/AIDS. This work line responds to a strategy for approaching medical healthcare and public health, which represents a key concept for the control of AIDS epidemics, as well as a multidisciplinary collaboration. Of course these initiatives take account of the maximum rigour with regard to the evaluation of available evidences in scientific literature for its efficient adaptation to our National Health System. They stem from the commitment of «the best available science» and the knowledges gathered in recent years from «scientific evidence-based medicine» as the best way to evaluate diagnostic tests and preventive and therapeutic interventions. In summary, this method is considered a key tool in the decision making process both clinically and of health policy.

Members of this Working Group are aware that current evidences about the management of chronic viral hepatopathies in patients who are coinfected by HIV are not enough to establish definitive recommendations since many of them are extrapolated from top-level scientific evidence from clinical trials where HIV-infected patients were excluded. However, we are sure in a near future, there will be results from studies on HIV-infected people which will lead to an improvement of the recommendations. For this reason, in this first edition, as it has been done in similar reports, we have adopted recommendation levels based on data coming from randomized and controlled studies with robust outcome variables (level A of evidence), from studies with substitute outcome variables or from cohort or case-control studies (level B of evidence) or from descriptive studies (series of cases) or experts' opinion (level C of evidence)[1]. In the future, this will allow adapt not only the contents of the recommendations but also the recommendation weight to the upcoming new scientific evidences. This first edition will be disseminated through two forms: the current one we are editing, where a wide crticial review of most relevant published studies or presentiations in scientific meetings is included, taking into account the conclusions from these studies and the considerations and recommendations for the clinical practice. It is basically a review document. A second form will be draw up for its dissemination through Scientific Journals and will gather the recommendations of clinical usefulness having sufficient consensus between the working group members. This will be the document of recommendations and consensus.

The Working Group for the elaboration of recommendations for viral hepatitis in HIV-infected patients has a vocation of continuity in a changing world where important scientific novelties are generated. These novelties should be critically evaluated by professionals so that these innovations can be eventually implemented in preventive and therapeutic practices as long as the foreseen impact is favourable. Moreover, this Working Group is aimed at identifying aspects requiring future investigations to be promoted through biomedical research funding agencies.

Finally, we think that both the report and the own make-up of the Group must be constantly open to new scientific input as well as different opinions regarding the health-care of patients coinfected by hepatitis viruses and HIV. Thus, we have established the appropriate ways so that the document's contents are submitted to the opinion of different proffesionals involved in the attention of HIV-infected patients prior to its dissemination in scientific media.

## Epidemiology of HIV and hepatitis viruses coinfections in Spain

Infections by hepatitis B and C viruses and HIV share the transmission mechanism of person to person by sexual contact as well as by intravenous and vertical transmission. They have long periods of latency and a trend to a chronic progression. There are differences regarding the transmissibility of the 3 viruses, sexual transmissibility of HBV being greater. Transmission of these viruses to the population is made by the contact between infected subjects and susceptible subjects.

In the case of hepatitis B, the existence of an immunized population is very important since it is neither infected nor susceptible. This population has become immunized due to a past and already healed infection or due to vaccination. This immunized population

has importance because it remains out the transmission chain.

In the case of HCV, there are also immunized subjects without viral replication which is detected as a result of a healed infection, either spontaneously or after treatment. However, this is a quantitatively less important population and, on the other hand, it does not remain out the transmission chain since reinfection is possible.

In developed countries, hepatitis A virus has a preferentially hydric transmission mechanism, yet it can also be transmitted through some sexual practices (mainly oro-anal) while parenteral transmission is not ruled out. Commonly, the adult population of developed countries get the infection by HAV after travels to developing countries and consumption of contaminated food[2,3].

The frequency of HIV and hepatitis viruses coinfection depends on three factors: prevalence of HIV infection, prevalence of infection by each one of hepatitis viruses, and coincidence of factors involved in both infections in the same subjects.

## HIV infection

It is estimated that between 100,000 and 150,000 HIV-infected people are currently living in Spain, which represents a seroprevalence of 3 per 1000. The distribution is very heterogeneous, and it is higher in males, in 20-40 year-old age groups and in urban sites[4,5]. Groups with higher prevalence levels are intravenous drug users (IDUs) (30%-50%), homosexual males (5%-15%) and stable sexual partners to IDUs or to people infected through other ways (5%-15%). Among women practicing prostitution who are not IDUs, the prevalence is below 2%.

## Hepatitis A virus infection

The incidence of HAV infection depends on the socio-economic and health level of each country. In the Spanish population older than 40 years, the prevalence of serum antibodies against HAV is very high, over 90%[6]. When we move to groups of younger people, a marked decrease in such prevalence is observed which is explained by a fewer probability among new generations of having been exposed to HAV due to better hygienic and health conditions of the country. As a result, more than a half of the population aged 25 to 29 years and over 70% of those aged 20 to 24 years are susceptible to HAV infection.

## Hepatitis B virus infection

There are 400 million people with HBV infection worldwide[7]. About 5% of the world popualtion are carriers of HBV. It is considered that 39% of transmission cases are associated with heterosexual contacts, 13% homosexual contacts and 14% IDUs. However, the mechanism of transmission is unknown in 33% of cases.

In the Spanish population aged 2 to 40 years, the prevalence of antiHBc is 4.5% although this prevalence is lower in the youngest and increases progressively with age so that it represents 9.8% in the 30-39 year-old group. Over 75% of people with anti-HBc have anti-HBs antibodies, hence pointing to a past infection leaving immunity; 3.1% of all population aged 2 to 40 years is immunized, namely, they have anti-HBs antibodies, while 0.8% have HbsAg. This marker indicates current infection and/or carrier status. Levels of HBV infection are greater among populations with high-risk sexual behaviour and in the IDUs as well. In a clinic specialized in sexual transmission diseases (Clínica Sandoval), the prevalence of some positive HBV marker was 70% among IDUs, 36% in homosexual males and 15% among heterosexual non-IDU population. 4% of homosexual males and 7% of IDUs have an active infection or they were HBV carriers (HbsAg+).

The antigenic subtype “ay” is the commonest among Spanish IDUs carriers[8]. This suggests that infections by the genotype D of the HBV are greater in this collective and, probably, in those HIV coinfected patients. This fact can have therapeutic importance since it has been reported that this subtype can be more sensitive to lamivudine[9,10].

In 1982, it was started a selective vaccination of people with risky behaviours, though the coverage degree attained in some groups is not higher than 20%. Between 1991 and 1995, vaccination programmes have been started in teenagers with coverages greater than 80% (table 1). In 2001, the first generations included in these vaccination programmes had reached 17 to 21 year-old, depending on the autonomous community. Thus it is expected that as they are getting to adult ages, significative changes will be probably seen regarding the epidemiology of hepatitis B in Spain.

TABLE 1. **Vaccination coverage against HBV since 1995-1996 in teenagers (10 to 14 years-old) in Spain**

| Year | Population | Vaccinated | Coverage |
|---|---|---|---|
| 1995-1996 | 425,123 | 353,414 | 83% |
| 1996-1997 | 434,141 | 354,476 | 82% |
| 1997-1998 | 449,735 | 379,551 | 84% |
| 1998-1999 | 412,413 | 332,699 | 81% |

## Hepatitis C virus infection

The main transmission way of HCV is the parenteral one. The sexual transmission, with the exception of some types of homosexual contacts, is not well-established and remains disputed[11,12]. In developed countries, acute HCV infections are associated with IDU (43%), sexual contacts with multiple partners or with an HCV infected partner (15%) or accidental exposure (4%). One in three patients does not recognize a clear risk factor at the time of diagnosis, although most of them have a risk factor other times or they are individuals from a very low socio-economic level[13]. HCV transmission via transfusion or blood derivatives in developed countries is under control nowadays. Yet until the 1990s, it explained 40% of HCV infections.

In the Spanish population aged 16 to 40 years, the estimated prevalence of antibodies against HCV is 2.1% with higher rates in males (4.2%) than in women (1.2%). This infection is associated with several risk practices related to the parenteral transmission of infectious agents such as the consumption of intravenous drugs. This is exemplified by the fact that IDUs and exIDUs have seroprevalence levels between 80% and 90%, while in those sexual risk collectives, as non-IDU prostitutes, the seroprevalence is lower than 2% (fig. 1)[14].

Overall, genosubtype 1b is responsible for over 75% of HCV infections, while those due to genosubtype 1a and genotypes 3, 2, 4 and 5 are less common, respectively. However, the frequency of infections due to genosubtype 1a and genotype 3 is greater among IDUs as well as, in general, among HIV-coinfected patients[15-19].

## HIV-HBV coinfection

*Dimension*

There is a clear association between HIV and HBV transmission, regarding both sexual and parenteral risk. Moreover, HBV acute infection is more prone to become chronic in HIV-infected individuals. Nevertheless, since hepatitis B chronification is much less common than in the case of hepatitis C, the prevalence of HIV-HBV coinfection is also much lower. It is estimated that in Spain such coinfection affects 5,000 to 10,000 people.

*Trend*

The number of new infections by HIV and HBV is clearly diminishing in Spain in recent years. This is due to the decrease in the

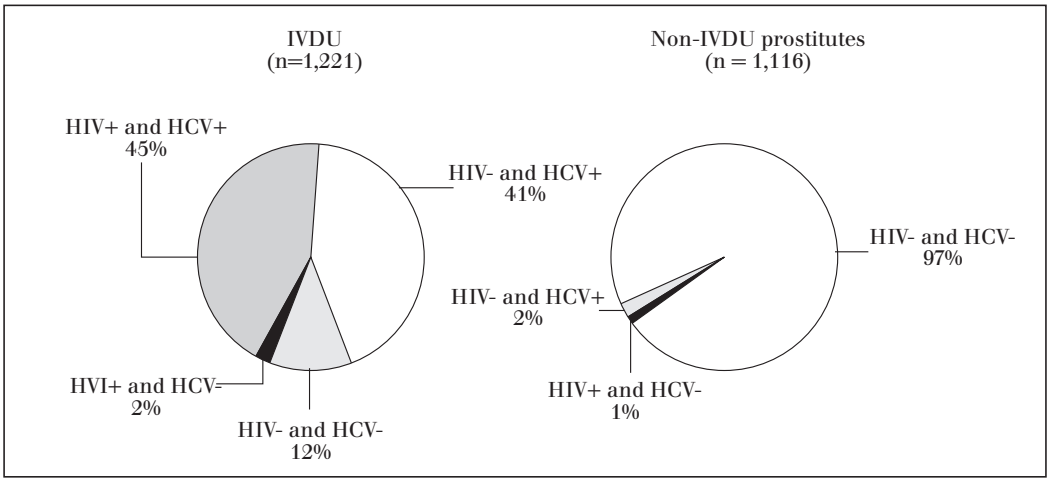


**Figure 1.** Infection by HIV and HVC in the two collectives. Healt Center Sandoval of Madrid.

number of new IDUs and to the decrease in the incidence of both infections among the main risk collectives. Moreover, we have to take into account the growing impact of the spread of HBV vaccination, though it is still not enough in greatest risk collectives. As a result of all this, the number of new HIV-HBV coinfections is much lower than at the beginning of the 1990s.

## HIV-HCV coinfection

*Dimension*

The prevalence of HCV infection among HIV-infected population varies in different geographic areas mainly on the basis of the distribution of those risk factors determining the transmission. There are also regional variations regarding the clinical features of coinfected patients such as age, gender, race or HCV genotype, which are related to the probability of response to treatment, and therefore they are variables to take into consideration when devising health policy strategies. Thus, in the USA the reported prevalence of HCV infection among HIV-infected patients is 16%, which varies according to risk factors; 83.3% corresponds to genotype 1 infections, 9% genotype 3 and 6% genotype 2[20]. In Southern Europe and especially among patients with a history of IDU, a high prevalence of infections by HCV genotype 3 has been reported[21,22].

In Spain, the prevalence of HIV-HCV coinfection is among the highest since both HCV and HIV infections are mainly associated with the consumption of intravenous drugs (fig. 2). Among HIV-infected IDUs, the frequency of HCV infection is still higher, over 90%. This contributes to the fact that HIV-HCV coinfection is found between 30% and 50% of people with a history of IDU. Since in Spain two in three HIV-infected individuals are IDUs, it can be estimated that the coinfection affects a total of 60,000 to 80,000 people.

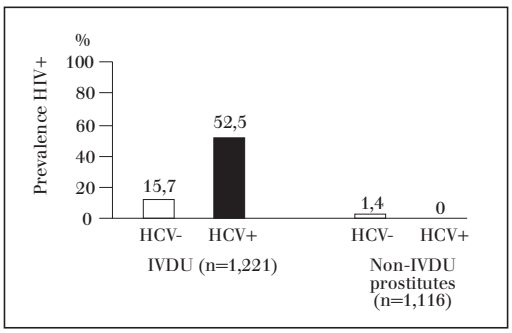


**Figure 2.** Prevalence of HIV infection according to the HCV status. Health Center Sandoval of Madrid.

The another group with a high prevalence of HIV-HCV coinfection is that of patients with hemophilia. On the contrary, in people who have got the HIV infection via sexual contact, the coincidence of both infections is a very uncommon fact.

In Spain, 65.5% of HIV-HCV coinfected patients have an infection by the HCV genotype 1, 22.2% genotype 3, 8.5% genotype 4 and 2.3% genotype 2[19].

*Trend*

As a result of the narrow association between HCV infection and IDU, the notable drop in the number of new IDUs cases occurred in Spain in the 1990s is very likely causing a great decrease in the number of new HIV-HCV coinfections[23]. Another factor contributing to a lower incidence of HIV-HCV coinfection, though to a lesser degree, is an adequate control of the parenteral transmission associated with blood transfusions or its derivatives. However, the longer survival of HIV-infected patients as a result of high activity antiretroviral treatments (HAART) means that there will remain a high prevalence of HIV-HCV coinfected people in the near future, many of them being potentially candidates for receiving specific treatment for HCV infection.

## Conclusions and recommendations on the basis on the epidemiology of the coinfection by HIV and hepatotropic viruses

1. The number of new cases of coinfection by HIV and hepatitis viruses is significantly decreasing, though a high prevalence of coinfections remains as yet. We must take into account that some of these coinfections may not have been diagnosed so far.
2. In the frame of the Spanish HIV epidemics, and on the basis of the high figures of coinfections by hepatotropic viruses, the morbility and mortality due to liver disease may increase in the next years.
3. HIV-infected people aged less than 30 years who has not been vaccinated against HAV can be highly susceptible and there is a hih risk of HAV infection associated

with some sexual practives or trips to endemic areas. Therefore, HIV-infected population must be regarded as target population for HAV vaccination (level C) (see vaccination section).

4. The number of people coinfected by HIV-HCV in Spain is very high and focuses mainly on IDUs and ex-IDUs. The high prevalence of HIV-HCV coinfection in HIV infected people in Spain justifies recommending a systematic study of HCV infection in these patients (level C).
5. A relatively high rate of infection by HCV genotype 3 in our HIV-infected population provides a better therapeutic chance (see «treatment of chronic hepatitis C» section).
6. HIV-HBV coinfection affects less people, though it is distributed both among IDUs and among the population at risk of sexual transmission. Vaccination of susceptible population could decrease the morbility of HBV coinfection. Therefore, it is recommended a systematic study of HBV infection in HIV-infected people (level C).

## Natural history of hepatitis B and C virus coinfections in HIV-infected subjects

### Introduction

Until 1997, HIV infection was almost invariably characterized by a progressive disease leading to the development of AIDS and death. Antiretroviral therapy (HRT), by avoiding the progression of the immunodeficiency, has had an important impact on the survival of HIV-infected people. However, this also has allowed the the development of common disorders in HIV-infected patients, with longer clinical latency periods and not so closely related to the immunodeficiency, as HBV and HCV infections. Taking into account the Spanish epidemics of HIV-infection, and on the basis of the high figures of coinfection by hepatotropic viruses, the mortality and morbality due to liver disease is likely to increase in the next years. In the last years, important advances in the treatment of chronic hepatitis have been observed. Therefore is an urgent necessity to know when and how to tackle the treatment of HBV and HCV infections in HIV-infected patients. From the natural history perspective, key questions to be reviewed in this chapter for therapeutic decision making are: how HIV infection affects the natural history of HCV and HBV hepatitis, respectively?, and how HCV or HBV infections influence the progression of HIV-associated disease?

### Impact of HIV infection on the natural history of HCV infection

In non-HIV-infected subjects, HCV acute infection uses to be asymptomatic in 60%-75% cases. In those cases with symptoms, these are not important and fulminant forms of HCV acute hepatitis are exceptional. Time needed between exposue and seroconversion is about 50 days, while 20% of patients with symptomatic acute hepatitis will present symptoms prior to the detection of antiHCV antibodies. In HCV acute infection, extremely high viral load values are observed before seroconversion, which decrease strikingly after seroconversion and, occasionally, below the detection level of the HCV qualitative PCR. In 15%-20% cases, acute infection resolves spontaneously, while it will become chronic in the remaining 80%-85%[24]. Just a small percentage, not well-established, will remove HCV infection after chronification. Reasons for this high percentage of active chronification are not well known yet it seems to be related to the type and intensity of immunologic response developed by the host. The genetic diversity of HIV and HCV constitutes a fundamental strategy used by the two viruses to survive and escape the immunological pressure they are submitted[25]. Due to this genetic diversity, only when the immunologic response, especially that involving cytotoxic T-lymphocytes, is sufficiently quick, vigorous and complete, viral replication can be controlled hence making it possible to eliminate HCV infection. In most patients, the immunologic reponse comes late or it is not strong and complete enough, allowing a suateined viral replication which, through the transcription errors in the continued cycles of viral replication, will lead to a *quasispecies* of HCV increasingly adapted to the host environment and, therefore, having a greater capacity to evade its immunity system (chronic infection). This elusive mechanism would be more effec-

tive in immunocompromised subjects. In a study on 1667 IDUs from Baltimore with a long-term follow-up (75% followed up for 14 years at least), HCV infection chronified in 90% of cases and the spontaneous eradication of the viremia was 5 times more frequent among Caucasian subjects in comparison with black subjects and 2 times more frequent in subjects having a negative HIV serology[26]. In a recent study, the prevalence of PCR HCV+ among antiHIV and anti-HCV positive patients was 91%, which probably pointed at a low rate of spontaneous eradication of HCV after exposition in coinfected patients[20]. It is possible that in HIV-infected patients, the risk of HCV infection chronification is increased due to a greater difficulty for erasing the acute or chronic infection spontaneously, hence contributing, partly, to the high prevalence of coinfection, though this is an aspect insufficiently studied so far (level B).

Out of the subjects with HCV chronic infection, 60%-70% have oscillating ALT values and 30%-40% have values within normal limits. HCV chronic hepatitis symptoms are scarce, even in people with an established liver disease. Even though most patients have HCV viremia detectable for ever, only 20% develop cirrhosis after 20-30 years of getting the HCV infection[24,27]. In the cases of cirrhosis, hepatocellular carcinoma develops in 2%-4% cases per year.

Progression of fibrosis depends mainly on the duration of HCV infection and the age at the time of getting the infection but also there are other influencing factors such as gender (more quick in males), alcohol intake over 50 g/day and HIV coinfection[24,26-30]. It seems that the transmission route does not affect the progression to cirrhosis, although it has been reported a greater level of progression in people infected via blood transfusions (maybe related to the higher size of the inoculation)[24]. It is important to mention that in studies in transfused patients, there is a trend to detect more frequently those developing disease and not those who, even getting the infection, do not develop the disease, hence overestimating the progression rate in this group[31]. There are other factors of the host and the HCV that could determine the seriousness of HCV liver disease and its progression. There have been reported 6 different HCV genotypes[1-6]. There is currently an open controversy on the role of the HCV genotype in the progression to liver fibrosis. On the one hand, there are data supporting a higher progression of the genotype 1b while others argues that it is hard to separate the independent effects of the genotype from other established risk factors such as the duration of HCV infection and the alcohol intake[25]. The genotype 1b is that being observed for a longer time in Europe and USA and, given the difficulties to determine the date of HCV first infection, there are doubts as to whether it provides HCV infection with greater clinical aggressivity or longer duration[25]. In HIV-infected subjects who are coinfected by HCV genotype 1, it has been reported a progression 3 times quicker (HR: 2.9; IC95%: 1.3-5.15) than in those who are coinfected by other genotypes[32].

The HCV viremia degree could be another factor associated with a higher rate of progression to cirrhosis. Its biological plausibility has not been confirmed by clinico-epidemiological studies as yet, unlike HIV infection. Patients with HIV and HCV infection have higher HCV viremia levels than those who are not coinfected, and it is inversely correlated with the number of CD4+ lymphocytes[33-35].

Several epidemiological studies have reported the negative impact of HIV infection on the progression of the HCV chronic infection to cirrhosis and hepatocellular carcinoma[24, 26,28-30,36-39].

In the above-mentioned Baltimore study, the incidence of end-stage liver disease, defined as the development of ascites, esophageal varices or encephalopathy, was relatively low: 0.3 per 100 people/year. Risk factors for developing end-stage liver disease were the age at the time of entering the study and an alcohol intake over 260 g per week. The low incidence of end-stage liver disease could be due to a very restrictive definition of this condition and to the fact that mortality secondary to other causes was high in a population who had practically not received ART[26].

In a cross-sectional Andalusia's study of 547 HCV infected patients enrolled between 1989 and 1994, 21% of them being coinfected by HIV, it was estimated that the proportion of subjects who had developed cirrhosis at 10 years of HCV infection was 15% for those being HIV positive and 3% among HIV negative patients[38].

In a study of cohorts with a mean follow-up of 13 years enrolling 122 HIV/HCV pa-

tients and 122 HIV-/HCV+ patients, there was a higher rate of progression to fibrosis in those being HCV coinfected and it was higher when the number of CD4+ lymphocytes was lower than 200 cells/µl. It was estimated that HIV infection shortens the evolution time to cirrhosis by 8 years (mean time of 26 years in coinfected and 34 years in non-coinfected). Alcohol intake was an independent factor of risk for progression to cirrhosis both in HIV coinfected and non-coinfected patients[29,30].

Progression to hepatocellular carcinoma was also quicker in HIV subjects as compared with HIV negative patients in other study performed in Spain[39].

In summary, most epidemiologic studies suggest that HIV coinfection speeds up the progression of HCV infection and the development of morbility/mortality due to liver disease in coinfected patients, and especially in patients with advanced immunosuprression (level B). This supports an active management of HCV chronic hepatitis in HIV-infected patients (level C).

### Efectt of HCV infection on the progression of HIV infection

It is important to differentiate the concept of increase of the morbility/mortality associated with HIV-HCV coinfection from that of accelerated progression of the HIV infection in coinfected people since, although both concepts are related, they are not synonymous and can have different therapeutic implications. Survival of HIV-HCV coinfected patients could be lower due to the specific lethality of HCV infection (end-stage liver disease) without relation to a greater loss of CD4 lymphocytes as a result of an immunological interaction of both viruses. Likewise, loss of CD4 lymphocytes could be accelerated in coinfected subjects and if HCV had no specific lethality, coinfected people would develop other opportunistic infections leading them to death. Until the availability of ART, it was harder to separate these two effects but it can now be observed if, in coinfected patients under ART, it is the HCV-related morbimortality due to end-stage liver disease which is increasing since patients live longer or it is the appearance of an immunologic impairment with a greater loss of CD4+ lymphocytes and a worse response to ART the main problem.

There is enough evidence to state that chronic infection and hepatopathy due to HCV increases the morbimortality in HIV-infected patients. And this is more notable at the HAART era since patients are more likely to develop liver pathology in parallel to their increased survival. In some hospital series, HCV hepatopathy is one of the main causes of death without association with immunodeficiency[40-50]. Greater pre-AIDS mortality in IDUs was already clearly associated with liver pathology prior to the HAART era[37,51]. In a Madrid´s hospital, uncompensated liver disease represented 8.6% of hospital admissions during a 4.5 years period. Out of these episodes, 87% were due to HCV infection, chronic viral hepatopathy representing the fifth cause of hospital death in HIV positive subjects[40]. The CHORUS study (Collaborations in HIV Outcomes Research USA), with a follow-up of 4,416 HIV-infected subjects, detected a 25% of mortality by causes other than AIDS between August 1997 and November 1998. Out of these, 72% were attributed to end-stage liver disease. In United Kingdom hemophilics at the pre-HAART era, liver disease-related mortality was 20 times greater in HIV negative subjects infected by HCV as compared with the general population and 94 times greater in males who were coinfected by HCV and HIV[37].

However, it is very disputed whether HCV coinfection speeds up the progression of HIV infection and the loss of CD4 lymphocytes. There is a worse prognosis and a quicker progression of HIV infection in coinfected subjects which could be related to a worse access to and a lower compliance of HAART, rather than the own HCV coinfection.

Other type of evidences suggest that the progression of HIV infection is not influenced by HCV coinfection. In Spain, until the end of 1996, the median of progression to AIDS from the first infection was 10 years, similar to other European countries, and without important differences between transmission categories with different HCV in- fection prevalences[52,53]. If it would accelerate the progression of HIV infection, we would expect to have seen clear differences in the progression to AIDS, drop of CD4 lymphocytes and mortality between the different transmission categories (level C). On the other hand, we would also expect to find geogra-phical differences regarding the progression rates in countries with similar health

systems but with different prevalence rates of HCV infection. This fact has not been observed either.

Works analysing th effect of HCV infection on HIV infection progression yield opposite results. Piroth et al described a higher progression of HIV infection in HCV coinfected subjects in the pre-HAART era[54]. In another more recent study of 812 HIV-infected patients with a known infection date, 89 of them being HCV coinfected, the same authors did not notice a greater immunologic progression, measured by the decrease of CD4 lymphocytes, but they did observe a higher clinical progression, defined a progression to AIDS, decrease of the Karnofsky index, weight loss and/or death from any cause[55].

Dorrucci et al, in a cohort of 416 people with known HIV seroconversion dates, 51% being coinfected by HCV, did not find differences as for progression to AIDS (HR 0.96) nor a count of CD4+ lymphocytes lower than 100 cells/µl[56].

In a recent study of 1742 HIV positive patients, HCV coinfection was not associated with a higher risk of opportunistic infection or death. HCV-infected subjects (45% of the cohort) were older, with a predominance of black patients, had used or used drugs more commonly and had a lower ART exposure. Although the univariate analysis showed a death risk higher (OR: 1.74) in coinfected subjects with a CD4+ lymphocyte count between 50 and 200 cells/µl, HCV infection was not associated with a greater mortality in the multivariate analysys which, otherwise, took into account the aforementioned differences between both groups. This suggests that coinfected patients were different from non-coinfected ones and that they had a lower probability of raceiving ART treatment[57].

Greub et al report an almost double rate of progression to AIDS and death (HR 1.7) in HIV positive subjects who are HCV coinfected, although it was not detected a significative increase of end-stage hepatopathy among coinfected patients (6 subjects; 0.5%) compared to non-coinfected ones (2 subjects; 0.1%). In coinfected subjects, there was an increase in the percentage of deaths due to HIV (3.5% vs 2.4%), deaths by overdose (2% vs 0), other death causes (2.6% vs 1%) and deaths by unknown causes (1% vs 0.4%). They also describe a worse recovery of the CD4+ lymphocyte count in reponse to ART. Therefore, the greater death risk among coinfected people was associated with the HCV infection rather than the presence of end-stage he-patopathy, and the authors suggest that the mechanism could be mediated by an acceleration of the loss of CD4+ lymphocytes[58]. However, the authors offer as an alternative explanation, both in the paper's discussion and in a response included in the correspondence section of another issue, that HCV coinfection could be a marker of greater progression rather than a causal factor[59]. The team of the hospital Carlos III of Madrid have described that HCV-HIV coinfected patients present a worse immunological and virological evolution and that these differences cannot be explained by a lower rate of ART indication nor by a lower compliance[60].

Finally, it is worthy of note that HCV chronic hepatopathy can modify ART efficacy and favour its toxicity. It has been reported a greater risk of hepatotoxicity by PI, especially ritonavir, in HCV coinfected patients (see later). The abnormal liver metabolism of some retroviral agents in HCV chronic hepatopathy patients could increase their maximum concentrations and thus any type of dose-dependent toxicity. For instance, there has been reported a greater risk of renal lithiasis with symptoms (OR: 2.8; CI: 1.1-7.7) in a study of HIV-infected patients with and without HCV or HBV hepatopathy treated with indinavir[61].

To sum up, there is evidence to state that HCV chronic infection increases the morbimortality of HIV-infected patients, although there are no definitive evidences showing that HCV infection accelerates the progression of HIV infection by increasing the loss of CD4+ lymphocytes. However, there are evidences suggesting that at the ART era, patients coinfected by HCV-HIV have greater difficulty of benefiting from this treatment (level B). Currently, it cannot be established a recommendation to treat HCV infection aimed at avoiding or speeding down the progression of HIV-associated disease.

## Impact of HIV infection on the natural history of HBV infection

Following the infection by HBV, patients develop a clinical picture of acute hepatitis that resolves spontaneously in most cases. 90% of children infected via vertical transmission and 5%-10% of infected adults will develop chronic hepatitis. The outcome of chronic hepatitis varies; most cases have a

bening evolution and only 15%-20% of the patients who got the HBV at an adult age will develop cirrhosis for the next 20 years. The rate of cirrhosis in people with HBV chronic infection is 1.5-2.5 per 100 patients/year. HIV affects the natural history of of hepatitis B increasing the risk of developing HBV chronic hepatitis. HIV-HBV coinfection has been associated with a greater probability of chronification, a greater risk of relapse of the HBV chronic infection and a slower removal of the HBe antigen (12%) as compared with HIV negatives (49%) at 5 years of follow-up.

It was initially reported a fewer hepatic inflammatory activity in patients with HBV chronic infection who were coinfected by HIV suggesting a more benign outcome of the hepatopathy[62]. However, it was revealed subsequently a greater clinical aggressivity of the hepatopathy due to HBV en HIV positive subjects as they had greater titers of HBV DNA, DNA polymerase, higher prevalence of serum Hbe antigen and greater expression of the HBc antigen in the hepatocytes, all of them being markers ofa higher HBV replication. Also, coinfected subjects have a lower rate of spontaneous serocnversion to anti-Hbe, which increases its transmisibility potential[63]. The greater activity of DNA polymerase is associated, in these patients, with lower levels of ALT suggesting a higher level of viral replication but a not so intense inflammatory activity of the liver as a reflect of an impaired immunological function[63].

A recent study about the influence of HIV on chronic hepatitis B in 132 homosexual males who were coinfected *de novo* suggest that HIV is associated with a HBV greater replication and with a greater risk of fibrosis but not inflammation, thus hypothesising that in spite of the HIV-related immunodeficiency, the progression of the fibrosis can happen when the inflammatory activity is minimal. Another finding of the study was that ALT levels were significantly lower in HIV positive than in HIV negative patients. The study excludes other viruses or hepatotoxic agents as alcohol. These observations are consistent with the pathogenesis of HBV at an immunological level in HIV positive subjects, where HIV-associated immunosuppression is associated with a lower hepatic inflamation[64].

The risk to develop cirrhosis was 4 times greater and the fibrosis degree was more intense in a study comparing liver biopsies in coinfected patients with those of HIV negative subjects. This suggests that the fibrogenesis process is eased in HIV positive patients, even having a lesser inflammatory activity, and for that reason a higher degree of hepatic fibrosis is observed.

To sum up, HIV infection does not prevent HBV infected patients from the development of advanced liver disease. On the contrary, it eases the progression of fibrosis. Now that ART allows a higher survival of HIV-infected patients, and therefore eases the development of HBV hepatopathy, HBV infection must be considered as a further condition to be treated in these patients (level C).

### Efectt of HBV infection on the progression of HIV infection

There are data suggesting that proteins from gene X of HBV stimulate HIV replication *in vitro*[65]. The progression of HIV-associated immunodeficiency, which is similar in different populations, with regard to the prevalence of HBV infection cotradicts the influence of HBV infection on the natural history of HIV infection. Cohort data point at the same way[58,66]. Finally, like HCV hepatopathy, HBV hepatopathy can be involved in a lower response rate and a greater toxicity of retroviral drugs, acting indirectly as a progression marker.

### Other factors influencing the progression of hepatopathies in HIV-infected patients

The consumption of hepatotoxic compounds such as alcohol and many drugs used in the treatment of HIV infection, especially ART, can influence on the gravity of the liver lesion[24]. The analysis of this influence, on the basis of its involvement in secondary prevention measures, will be discussed in the «prevention» section.

### Conclusions and recommendations of the basis of the natural history of the coinfection by HIV and hepatotropic viruses

1. ART has reduced the progression of HIV infection and has allowed the development of other diseases with longer clinical lathency periods such as HBV and HCV liver diseases which are not as closely related to the immunodeficiency as other opportunistic disorders defining AIDS (level B).

2. The impact of HIV on the natural history of HCV infection is relatively well-established and there is enough evidence to suggest that HIV speeds up the progression of HCV infection to serious liver disease and the development of cirrhosis with shorter lathency periods in HIV positive subjects (level B).
3. HCV infection also influences HIV infection and there is a greater morbimortality due to hepatic pathology in coinfected subjects. It remains disputed whether HCV coinfection accelerates the progression of HIV infection; there is no clear consensus and it is possible that differnces observed owe to different designs, inclusion criteria and analysis performed in different studies.
4. HIV coinfection modifies the natural history of HBV infection, making the infectivity period longer and conditioning a greater progression to hepatic fibrosis (level C).
5. From a practical point of view, it should be considered the management of hepatopathy in those patients with HIV infection and chronic hepatitis B or C on a broad sense (primary prevention, control of modifiable progression factors and antiviral treatment) (level C). This recommendation is fundamentally based on the different natural history of chronic viral hepatitis in coinfected subjects, with a higher risk for the development of hepatic disease and a subsequent greater morbimortality.

## Diagnosis of infections by hepatitis viruses in HIV-infected patients

### Hepatitis A virus

As it happens with the rest of viral hepatitis, the diagnosis of HAV infection is serological. Objectives pursued in this case are diagnosing the acute infection or knowing if the patient is susceptible to the virus, taking account of the possibility of vaccination. The criteria used in the general population is also the application in HIV-infected patients. The following considerations are to be taken into account in our milieu:

1. It is considered that Spain has a moderate HAV endemicity, yet it is clearly decreasing in recent years, thus approaching us to the standards found in our socio-economical circle.
2. HIV-infected patients have a higher risk of getting the infection regarding the general population, especially in homosexual patients. In homosexual patients, it is also possible the primary coinfection by both viruses, HAV and HIV.
3. There remains the possibility of a greater HAV-related morbility in those patients with an advanced AIDS stage.
4. It has been suggested that the risk of development of fulminant hepatitis is greater in patients suffering from chronic liver disease, which is not uncommon in HIV-infected patients, either due to drugs or to the infection by other hepatotropic viruses highly prevalent in this population group (HCV, HBV).
5. At present, there is an available effective vaccine against HAV.

*Serological diagnosis of HAV infection*

Molecular and culture-based techniques lack applicability here. The diagnosis is serum-based exclusively.

The diagnosis of an acute infection is performed by means of the detection of IgM antiHAV antibodies. Commonest technique is capture-ELISA, for which reliable commercial systems are available. IgM antibodies coincide with symptoms and the fecal excretion of the virus and they become negative, in general, after 2-3 months, yet in some cases can be detected for a longer period.

The detection of IgG antibodies is useful to know the immunity status of the patient and to determine the opportunity to vaccinate him/her. IgG antibodies develop progressively throughout the acute phase of the infection and remain for ever. There are commercial systems (ELISA) that ease a reliable detection of these antibodies. Highly immunodepressed HIV-infected patients ($< 100$ lymphocytes CD4+/µl) can display a falsely negative serology against HAV[67].

### Hepatitis B and delta viruses

Diagnosis of HBV infection relies on the detection of the HBV surface antigen (HbsAg) in patient's serum and in the determination of anibodies against the «core» (anti-HBc) and against HbsAg (anti-HBs). The finding of anti-HBc antibodies belonging to the IgM class is usually

regarded as indicating an acute primary infection while the finding of anti-HBs antibodies is regarded as a marker of resolution of the infection and immunity against reinfection. In chronic carriers, the study of the system made up by the «e» antigen of the HBV (HBeAg) and its specific antibodies (anti-HBe) as well as the detection of the viral genome in the serum, either by molecular hybridization or genomic amplification (replication markers), are useful tools to delimit the characteristics of the virus-host relationships at every time. HBeAg is a marker of active replication and infectivity and is associated with high serumtiters of HBV DNA. HBeAg seroconversion to anti-Hbe is associated with the disappearance of HBV DNA from the blood and clinical improvement. In some cases, HBV has a mutation in the pre-core region that avoids the expression of HBeAg. In these cases the patient will show active liver disease with positive HbsAg, serum detection of HBV DNA and serum negativity of HBeAg.

With regard to the specific diagnosis of HBV infection in HIV-infected patients, some considerations must me taken into account:

1. A higher chronification rate, due to their cell immune response's deficiencies and, for the same reason, their higher trend to remain as chronic carriers with high viral replication.
2. The possibility, not demonstrated but reinforced by indirect data, that deep cell immunodepression can ease the reactivation of «latent» HBV in individuals with previous immunity markers.
3. The circulation of HDV in this group, especially in IDUs.
4. The possibility of vaccinating patients who are not coinfected by HBV and the lower rate of specific immune response they have.

*Use and interpretation of serological markers of infection*

*Diagnostics tests.* In HIV-infected patients, serum markers of HBV infection are applied according to the general diagnostic recommendations and techniques[68]. Commercial tests and systems used to detect these markers are based on enzyme-immune assays and, in general, they are reliable. Molecular methods detecting HBV DNA are based on the amplification of the hybridization signal (Hybride capture `[Digene] or ramified DNA [Chiron-Bayer]) or PCR amplification (Roche).

As long as an acute or chronic HBV infection is detected in an IDU patient, specific tests must be carried out for the diagnosis of the coinfection or overinfection by HDV. In these cases, the detection of IgM anti-HDV can be used as a marker of coinfection or acute overinfection, while the detection of total anti-HDV or IgG will be useful to identify HBV chronic carriers who are HDV carriers also. On the contrary, the detection of the HDV antigen has low efficiency leves and is not recommended. The detection of HDV RNA is a complex technique with scarce clinical usefulness.

*Some special situations in HIV-infected patients:*

1. In HIV-infected patients, it is not unusual to detect the *coexistence of HbsAg and anti-HBs* in the serum of some patients during diagnostic systematic studies. In most instances, both markers are confirmed when performing the corresponding neutralization tests and, therefore, the pattern points to the presence of HBV active infection with anti-HBs. It is speculated that HBV can establish a latent infection in some non-identified tissue and that, under a deep cell immunosuppression, the latent virus could reactivate and reestablish the production of HbsAg and whole particles, although this possibility has not been clearly demonstrated[69]. It is known that this serum pattern can be accompanied with positive markers of viral replication and even HBV-related liver lesions.

   The coexistence of the two markers may also owe to the presence of HBV strains with significative mutations at the genome region where immunodominant epitopes of the HbsAg antigenic determinant «a» are codified. Some of these variants are not recognized by anti-HBs antibodies induced by a previous infection by a wild HBV strain or by vaccination. Thus, this second infection could generate a pattern of HbsAg and anti-HBs coexistence in the patient's serum. This type of mutants has been found in Spain, especially in IDUs, and thus such possibility must be considered[70].
2. The *detection of total anti-HBc with lacking HbsAg and anti-HBs (anti-HBc*

*alone* pattern) is very common in HIV-infected patients, especially in IDUs. For instance, in IDU patients with a high prevalence of HBV infection (70% in the Spanish cohort of the Sandoval Center), up to 30% of them will display an antiHBc alone pattern. The interpretation of this pattern depends on the probability of getting a HBV infection.

In the general population, having a low prevalence of HBV infection, this pattern uses to be uncommon and mainly due to an unspecific reaction of the anti-HBc detection techniques (false positive). In fewer cases, this will correspond to silent chronic infections, recent acute infection under remission (window stage) or an old and resolved infection with a decrease of anti-HBs antibodies down to undetectable levels. In order to clarify the actual scenario, it is recommended to determine the viral DNA by means of highly sensitive methods and/or to assess the future development of antiHBs on a spontaneous manner or its apparition kinetics after a vaccination dose against HBV[71].

However, in the population with a high probability of being infected by HBV, as in HIV positive patients, the antiHBc alone pattern is relatively frequent and in general it indicates an immunization status due to active or past (true positive) HBV infection and, therefore, there is no vaccination indication. In a classical study it was demonstrated that HIV coinfected patients with a past HBV infection are prone to loose eventually the antiHBs marker at a greater frequency than the population without HIV infection, and this may explain the greater prevalence of the antiHBc alone pattern in HIV positive patients[72]. For unknown reasons, this pattern uses to be more common when there exists a HCV chronic infection and is associated with a more severe hepatic lesion than those cases with HCV chronic infection without HBV infection markers[73]. To date, the best evidence showing that the antiHBc alone pattern indicates immunization against HBV in people with a high prevalence of HBV infection is the study performed by Quaglio et al[74]. Among 497 patients with this pattern who had an IDU history (31% HIV+), after 4 years of follow-up with an annual serologic determination, none case of acute hepatitis was observed nor the *de novo* apparition of HbsAg. The antiHBc alone pattern remained in 81% of the cases and in 19% of cases antiHBs developed likely as a natural booster effect. In contrast, in an IDUs control population, who were susceptible to HBV infection, there was an 11% seroconversion cases during the same period. These data support the protection against HBV infection which is associated with the serum anti-HBc alone pattern as well as the absence of vaccination indication in these cases when it is a population with a high HBV infection prevalence, even if they are coinfected by HIV. Another study of a cohort of 240 patients has recently confirmed these results[73] (level B). However, it is important to remind that in these patients the antiHBc alone pattern means immunization but it does not differentiate active from passive infection. In the Swiss cohort, this pattern was frequently associated with low level HBV viral replication, which was demonstrated by means of HBV DNA serum determination, and therefore at risk of reactivation or progression of the HBV infection[75]. It is important to bear in mind this possibility since these patients may have exacerbations of hepatitis B in different situations associated with HIV infection, for example at the beginning of ART, withdrawal of an ART regime including lamivudine or after the development of resistance mutations to lamivudine[76,77].

*Evaluation and virological follow-up of the antiviral treatment in chronic carrieres*

At the time of assessing the onset of antiviral therapy in a HBV chronic carrier, the only clearly established predictive factor is the fact that the patient has or has not selected HBV pre-C defective strains prior to starting such treatment, as these strains are strongly resistant to interferon treatments. Currently, we do not have suitable techniques to deal with the molecular detection of these strains, apart from highly specialized laboratories. However, the very detection of viral DNA in a HbsAg carrier having anti-Hbe antibodies is suggestive enough of infection by a pre-C defective strain.

Once started therapy, the quantification of viral DNA eases a precise follow-up of its effect on virus replication. Quantitative molecular hybridization methods, which are able to detect concentrations as high as 1 pg/ml, are very appropriate for this purpose since they offer a more accurate and reproducible quantification.

In the last months, lamivudine has emerged as a potentially strong alternative to interferon in chronic hepatitis B. However, the apparition and selection of variants developing resistance to the drug during the therapy is a known problem. In the market, there is a reverse hybridization method (LiPA) designed to detect the development of the main mutations associated with lamivudine resistance. Thus, this technique may be useful in the follow-up of patients treated with this agent, though precise recommendations and interpretations are not clearly established as yet.

**Hepatitis C virus (HCV)**

The diagnosis of HCV infection is mainly serologic by detection of specific antibodies (anti-HCV). Serum presence of anti-HCV reflects a previous contact with the virus and indicates, in most cases, a persistent infection. Even though the presence of specific antibodies may be, occasionally, result of a past and resolved infection, these antibodies do not protect against potential reinfections. The direct detection of the virus by means of molecular diagnosis techniques or antigen detection is an additional diagnostic aid[78].

This diagnostic approach, which can be applied to all the population, is valid in HIV seropositive patients. But there are some differential characteristics to bear in mind at the time of selecting diagnostic tests for HCV detection in this population.

1. The prevalence of HCV infection in HIV infected people is much higher than that seen in the general population (9%-40% vs 1%-2%), while in some coinfected populations such as IDUs or ex IDUs and hemophilics it reaches 90%, which means that the positive predictive value of the anti-HCV antibody detection tests is very high. As a result, the determination of these antibodies must be systematically performed in HIV-infected patients. In those patients whose screening tests are positive for antiHCV antibodies who belong to high-risk groups of HCV infection, in general there will be no need to perform confirmation tests to determine the HCV coinfection (level C).
2. Apart from advanced HIV infection stages, humoral immune response will be normal in these patients, during both acute and persitent infection. Thus it is not expected that diagnosis based on the detection of antiHCV poses problems in the majority of HIV-infected patients[79].
3. The greater risk of repeated HCV exposition will make reinfections as well as multiple infections by strains belonging to different genotypes to be more frequent in these cases too. Therefore, it is important that this circumstance is taken into account when thinking of and interpreting HCV infection diagnostic tests in HIV-infected patients.
4. The diagnosis of chronic infection by molecular techniques or direct detection of the virus will probably be easier since the blood concentration of viruses uses to be higher than in immunocompetent patients.
5. The greater risk of exposition to the infection of many patients makes it advisable to consider some specific questions regarding the follow-up of those who are not infected yet and the interpretation of the results from some techniques.

*Detection of antiHCV antibodies*

*Descriptin of the techniques.* The techniques for the detection of antiHCV antibodies are categorized as screening and confirmation methods. Both have diagnostic limitations since do not allow the differentiation between acute (acute or chronic) and resolved infection, results can be negative at the initial period of the infection (up to 3 to 6 months after the exposition), they can lead to false negative results in immunocompromised patients such as an advanced HIV infection, humoral immunodeficiency, post-transplantation or renal insufficiency and even there can be false positive results when screening tests are used in low risk situations or in patients with autoimmune diseases.

Screening tests mainly include 2$^{nd}$ and 3$^{rd}$ generation ELISA, which have better sensitivity and specificity than 1$^{st}$ generation ELISAs and also they shorten significantly the acute infection´s window period. As prevalence of HCV coinfection is very high in HIV-infected patients, the positive predictive value of modern ELISA is also very high (table 2). Although in some laboratories the 3$^{rd}$ genera-

TABLE 2. **Detection of HCV antibody by ELISA**

| ELISA | Sensitivity (%) | Positive predictive value (%) | |
|---|---|---|---|
| | | Low prevalence | High prevalence |
| 1st degeneration | 70-80 | 30-50 | 70-85 |
| 2nd generation | 92-95 | 50-61 | 88-95 |
| 3rd generation | 97 | 25 | Non-established |

tion tests are preferred over 2nd generation ones in order to screen high-risk populations, their positive predictive value is not well-established and thus the benefit from its application in HIV+ patients is not clear.

Confirmation techniques include the recombinant immunoblot assay (RIBA) and the line immunoblot assay (LIA), in which antibodies react with antigens placed on separate bands over a solid support. The confirmation tests lead to high specificity levels but they must not be used as initial diagnostic tests. They must be used to confirm the diagnosis in those cases having a positive ELISA result and low-risk of infection.

*Utilization conditions.* Detection of antiHCV by ELISA techniques is perfectly accessible for any laboratory working on microbiologic diagnoses. It will be convenient to choose those methods having a higher sensitivity to detect antibodies against non-structural protein-3 (NS3) of the HCV, as these use to appear earlier[80]. Experience indicates that in patients with a risk history (high prevalence), it is not necessary to perform systematically immunoblot techniques to corroborate those antiHCV positive samples, which is especially the case in those HIV+ patients with an IDU history or hemophilics[81]. The usefulness of the tests of confirmation of antiHCV antibodies is limited, in HIV+ patients, to the following uncommon situations: a) patients without an IDU history, hemophilia or blood derivatives transfusions prior to 1990; b) when screening techniques give doubtful results[82]; and c) when the tests for direct detection of the virus (see later) are negative in a patient having a positive result in the screening techniques.

The interpretation of the immunoblot techniques for the confirmation of antiHCV antibodies regards as undetermined those samples having reactivity against antigens from a unique region of the viral genome. This can happen during the early stage of seroconversion in the primary acute infection and, in such a case, it uses to generate anti-NS3 patterns or anti-core alone patterns and it is always accompanied by viremia that is detected by direct detection techniques. If direct detection techniques are negative, they indicate that the undetermined result owes to non-specific reactions and they rarely reflect the actual presence of antiHCV (false positive)[82].

Finally, even though the quality of commercial systems available for the detection of anti-HCV is high, it is important to remind that in HIV-infected patients there remains the possibility of facing samples taken during the acute stage of the primary infection[83]. If such a circumstance is suspected, the most sensitive proofs must be sought and, if they are negative, the test must be repeated using other samples at different times. If there were a diagnostic urgency (e.g, when one is going to consider administering treatment for HCV acute infection), it is possible to perform a method to detect the virus directly (see later).

*Direct detection of hepatitis C virus*

*Description of the techniques.* HCV direct detection is mainly performed by molecular methods, in general commercial systems. Commonest methods are PCR-based ones (Roche's Amplicor), with qualitative and quantitative versions. Qualitative techniques are usually more sensitive than quantitative ones. Recently, another technique to detect the genome different from PCR tecniques has been commercialized. This is the Versant TMA (transcription mediated amplification) system which is commercialized by Bayer[84]. Its main characteristics are summarized in table 3.

Regarding quantitative techniques, there are two commercialized systems: PCR com-

TABLE 3. **Characteristics of HCV direct detection tests**

| | PCR Amplicor Cobas 2.0 | Versant TMA |
|---|---|---|
| Sensitivity | 100-1000 copies/ml (20-200 IU/ml) | 50-100 copies/ml (10-20 IU/ml) |
| Genotypes | 1, 2 (3, 4, 5, 6) | 1, 2, 3, 4, 5, 6 |
| Main advantages | Greater experience in general<br>Higher level of assumption of the technique by the laboratories | Greater sensitivity<br>Greater discrimination regarding the therapeutic response<br>Low contamination risk |

petitive amplification (Monitor, Roche) and bDNA system signal amplification 2.0 (Versant, Bayer). The PCR method has been clasically considered as much more sensitive than the bDNA method, as the latter was able to detect 200,000 copies/ml as a minimun and the former had a lower limit of 1000 copies/ml. However, when an international units pattern has been available, it has been possible to notice that such differences are not so great since quantities were not equivalent for both systems. On the contrary, bDNA is more robust and reproducible, quantifies better genotypes other than genotype 1 and displays a greater lineality interval. It has been recently commercialized a new version of the Bayer method (bDNA 3.0) for which its manufacturers point at a detection limit of about 2500 copies/ml (factor of conversion of copies in IU/ml 1/5.2 according to Bayer Diagnostics manufacturer), though there is not a wide experience so far.

Recently, an ELISA method able to detect serum HCV by capturing the core protein through monoclonal antibodies after breaking the viral particles has been marketed. In its initial version, the technique was only able to detect the viremia during the window period of the acute infection or in those rare cases where there is no antibody response to that antigen[85]. The 2nd generation, commercialized very recently (trak-C, Ortho Clinical Diagnostics), is able to detect viremia levels equal to or higher than $5 \times 10^4$ IU/ml (1.5 pg core antigen/ml) under the presence of antibodies, which would make it possible to detect and quantify the virus in most chronic carriers who are not submitted to antiviral treatment and, consequently, it might be widely used as a diagnostic technique[86].

*Application conditions.* Tests for direct detection of the virus have two main indications: diagnosis of acute infection at the window period (if there is a true diagnostic urgency) and the evaluation of patients who are candidates to receive specific antiviral therapy. There will be the need to employ the techniques of direct detection in order to diagnosing a HCV infection in those patients with suspicion of a falsely negative antiHCV serology (high-risk populations with an increase in the levels of transaminases) or for the diagnosis in case of suspicion of vertical transmission.

In patients with suspicion of HCV acute infection, the direct detection of the virus is indicated if there is any antiHCV negative case who has a risk of having suffered an exposition to the virus for 6-8 weeks before taking the sample. During the window period, the blood concentration of virus uses to be very high (equivalent to $10^6$-$10^8$ copies/ml as measured by quantitative PCR) and thus the sensitivity of the technique to be used will not be a limiting factor. Both the detection of HCV core antigen by ELISA and any qualitative procedure for detecting the viral genome (PCR, etc.) are useful in this situation. But the window period of the acute stage of HCV infection results eventually in with the development of specific antibodies, with the exception of humoral immunodeficient patients (highly advanced AIDS). Consequently, it is possible to opt to confirm the window periods by corroborating the antiHCV seroconversion in a sample taken two months later. This way the application of the HCV direct detection techniques to the diagnosis of the window period only makes sense if there exists a true diagnostic urgency (or when an early treatment is to be considered).

In those patients who are eligible to receive specific antiviral treatment, the meaning of the test is to check that there is a viremia before starting the therapy, to ease the knowledge of the viral genotype and to provide a basis to assess subsequently their response to the treatment. During chronic infection, blood viral concentrations use to be within the $10^5$-$10^6$ copies/ml range, so methods should be used whose analytical sensitivity matches these concentrations[87]. PCR-based genome amplification techniques are more common, yet the new bDNA versions satisfy widely these needs. It is important to highlight that sensitivity of PCR methods depends, fundamentally, on the extraction procedure used; highly sensitive methods usually face more complex extraction procedures with multiple manipulations of the sample. This situation increases the risk of contamination, limits the processing capacity of the laboratory and can affect negatively the method itself. The new ELISA procedure to detect antigen can be applied in such a circumstance, although it is not able to ease the genotypification of the detected virus[88].

It has been suggested that the concentration of virus at the serum prior to starting the treatment correlates with the subsequent thera-

peutic response and can be regarded as a useful data in order to choose the most appropriate therapeutic regime[89]. To sort out the differences from the results observed by using different quantification techniques to determine the RNA HCV, it is recommended to express the result in the form of International Units/ml. Yet intercomparative studies demonstrate that, in the best conditions, the intrinsic variability of results is not lower than 0.5 logs above and below the obtained value (European Union Quality Control Concerted Action, manuscript under preparation). This means that a quantitative result of, for instance, $1.5 \times 10^6$ IU/ml will actually reflect any concentration within the range $5 \times 10^5$ to $4.5 \times 10^6$ IU/ml, which must be taken into account both at the time of notifying the result and when interpreting it on the basis of adopting decisions that may affect the patient's treatment. In the proposed example, the extreme values of the range are different in the prognosis of the response with regard to the HCV viremia ($>$ or $<$ 800,000 IU/ml) as well as in the indication of the treatment duration. It has also been suggested that the decrease of the HCV quantitative viremia at 4 or 12 weeks as a response to anti-HCV treatment can mean the continuity or interruption of the therapy[90-92]. In order to mitigate the intrinsic variability effect of the technique, it is recommended that the follow-up samples from a given patient, whose viral concentrations are to be compared, should be analyzed in parallel within a same assay, regardless of the used technique (level C). Finally, the quantification of the core antigen by the new 2nd generation ELISA is able to accurately predict the presence or absence of response to treatment at earlier treatment stages, which would mean a broader spectrum of this type of techniques[93,94].

*Genotypification of HCV strains*

In Spain, genosubtype 1b is responsible for over 70% of HCV infections, both in chronic hepatitis patients and in blood donors[15,16]. But this is not the case among IDUs collectives where infections due to genosubtype 1a and 3 are significantly more common[17]. Since available antiviral therapies are more useful for patients infected by the latter genotype, the determination of the HCV genotype can be an important aspect to be considered at the time of treating patients with HIV coinfection[19,20].

The determination of the genotype can be made by different methods, and it is always required the previous amplification of a selected fragment of the viral genome by means of PCR. In general, the 5′-non-codifying region (5′-NC) is most used as target. Currently, the technique of reverse hybridization with specific probes for different genosubtypes (Line Probe Assay, LiPA)[95] is the most common, although the analysis of the polymorphism of the fragments obtained after digestion with restriction endonucleases (RFLP), the amplification with specific initiators of genotype and the obtention of the consensus sequence by direct sequencing of amplification fragments are all valid alternatives. In IDUs, due to their risk of repeated exposure as well as possible non-specific reactions, it is possible to find mixed LiPA patterns. In such cases, specific serotypification can help solve the conflict[96].

*Virologic follow-up of the antiviral therapy*

Antiviral therapy of HCV infection has the chief goal of eradicating HCV. The virological follow-up of the therapy is aimed at evaluating the repercussion of the treatment on the viral replication and it is required the employment of direct detection techniques. After starting treatment, blood levels of virus can decrease significantly, without meaning a subsequent clearance of the viremia. As consequence, methods not having a high sensitivity degree can lead to false negative results in samples harbouring low virus levels, thus providing the false impression that the viremia has been cleared. It is not rare to see during the follow-up a decrease in the blood virus levels down to $10^2$-$10^3$ copies/ml in patients who are not to subsequently clear totally the virus, and thus is useful to employ methods allowing to detect low concentrations of the virus. Thus, there could be recommended qualitative techniques (cheaper and more sensitive) for the monitoring and making therapeutic decisions during the antiHCV therapy. But the degree of modification of the HCV viremia after starting the antiHCV treatment can define the long-term result of the therapy, especially with regard to the negative predictive value of less significant modifications (detectable viremia with a decrease of less than 1 log at the month of treatement or less than 2 logs at three months) on the final response[90-92]. Some authors have proposed to

substitute qualitative by quantitative techniques for monitoring the antiHCV therapy.

Currently, there is no consensus over the monitoring techniques more suitable for the follow-up of antiHCV therapy. These will be chosen according to the Center's possibilities, the criteria establised regarding the continuity or not of the treatment and the time the response is being evaluated. In general, qualitative tests are indicated for the diagnosis of active viral replication in order to consider the antiviral treatment and to check the response. Quantitative tests are indicated to evaluate the probability of response, both pre-treatment and during the treatment.

### Conclusions and recommendations for the diagnosis (algorithm fig. 3) and the follow-up of HCV infection in HIV-infected patients

1. Diagnostic strategy will be based on the following first-line tests:
   - Detection of antiHCV by immunoenzyme techniques. It is advisable to choose methods with high sensitivity for the detection of antiNS3. We must check a positive result by immunoblot only in doubtful result samples, which is not generally needed in HIV+ patients with a high risk of HCV exposure (IDUs, hemophilics, etc.).
   - Virus direct detection when it is indicated the search of window periods or in casese of seronegative hepatitis with a high probability of HCV infection. Minimal sensitivity requirement: equivalent to $10^5$ copies/ml. The detection of the core antigen by ELISA can be used for this purpose.
2. The evualuation of candidates to antiHCV treatment will be based on:
   - Direct detection of the virus by molecular diagnosis methods. Minimal sensitivity requirement: within the range $10^3$-$10^4$ copies/ml. The ELISA techniques for the detection of the core antigen could be useful in the near future.
   - Genotypification of the detected virus by LiPA, RFLP, PCR with specific initiators of genotype or direct sequencing of amplification fragments. When it is of interest, infections by multiple genotypes detected by LiPA could be confirmed by typification of accompanying antibodies.
   - Optionally, quantification of viremia by molecular diagnostic quantitative techniques. Some professionals prefer this option because it permits a more detailed follow-up of the antiviral agents effect. The information and interpretation of the result will be made according the variability attributable to each quantification method, so it is important that this data is fairly well evaluated and known by the user.
3. The virologic follow-up of the antiviral therapy will be made by:
   - Direct detection of the virus by molecular diagnostic methods. Minimal sensitivity requirement: within the range $10^2$-$10^3$ copies/ml.
   - Optionally, quantification of the viremia by molecular diagnostic quantitative techniques, with the aforementioned considerations regarding the information and interpretation of results. If possible, to be compared samples will be analyzed in parallel within the same assay.

## Clinical management of viric hepatopathies in HIV-infected patients

### General aspects

Indications regarding management of hepatopathies in HIV-infected patients must be individualized according to each patient's situation. Firstly, an exact diagnosis of each situation must be performed.

In any HIV-infected patient, it is necessary to perform at the onset of the follow-up a study of transaminases and antiHCV, HbsAg, anti-HBc, antiHBs and IgG HAV serologies. Moreover, there will be assessed the existence of modifiable factors responsible of hepatopathy or its progression, especially alcohol consumption and consumption of drugs and medicines.

In HbsAg+ patients, there will be performed the following studies: DNA HBV, HBeAg, anti-HBe and anti-HDV in serum samples, abdominal ultrasonography and the indication of antiviral therapy will be assessed according to the existing criteria. Recommenda-

tions for secondary prevention of hepatic damage will be made.

In patients with anti-HCV and normal levels of transaminases, it is recommended a monitoring of these levels.

In patients with anti-HCV and persistent hypertransaminasemia, other causes of hepatopathy should be ruled out and it must be performed a qualitative PCR-HCV. If the patient is a candidate to receive treatment, it must be performed: genotype, quantitative PCR-HCV and it is important to assess the performance of a liver biopsy. The secondary prevention of hepatic damage is always recommended.

In antiHCV negative, HbsAg negative patients with hypertransaminasemia, it is recommended to rule out other pathologies, including ART-related toxicity. If the patient is highly immunodepressed, he/she can have a false negative antiHCV and in such a case it is recommended to perform a qualitative PCR-HCV.

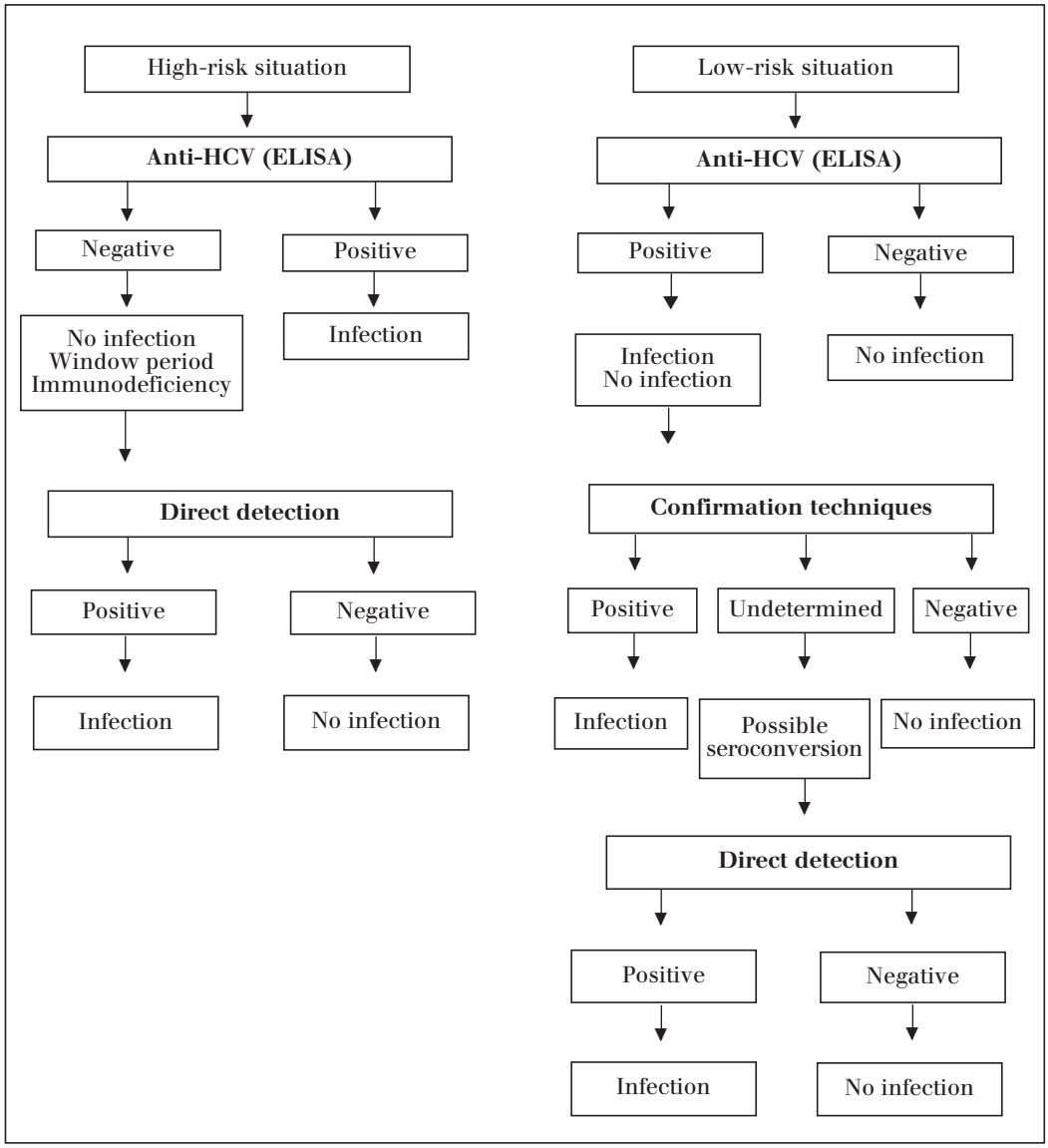


**Figure 3.** Diagnostic algorithm of HCV infection.

In patients with cirrhosis it is recommended the monitorization of liver biology and the study of coagulation, determination of alphafetoprotein and abdominal ultrasonography every 6 months. If there are signs of portal hypertension, it must be performed an upper endoscopic study to assess the existence of esophagic and/or gastric varices and thus to establish the treatment criteria of portal hypertension.

## Prevention of viral hepatitis: vaccines and interventions to decrease risk behaviours

*Primary prevention of transmission*

If the patient is HCV negative, he/she must be informed to avoid risk practices easing the transmission[97] (level C).

If the IDU patient quits the IV use, then the main transmission path of HCV is eliminated. Those patients maintaining this practice must be told that the hygienic measures can decrease the risk (not to share nor to reuse syringes, needles, water not any component used in the preparation of the drug). There have been promotes controlled exchange programmes involving needles and syringes in IDUs patients. Despite its benefits, it is not clear that such programmes have any impact on decreasing HCV seroconversion[98] (level C).

Although there are doubts that cocaine inhalation eases HCV transmission, subjects performing this practice must be informed not to share material. It is also important to warn of the potantial risks of acupuncture, tatoos and piercing, especially when these are not performed by professionals (level C).

Although the risk of HCV sexual transmission is low, HIV+ patients should use barrier protection methods to reduce the risk of sexual transmission diseases[97] (level C).

There is no specific immunoglobulin nor postexposure vaccine, unlike HBV infection.

In patients with risk of sexual transmission, especially if they are susceptible to HBV or HAV infection, it is important to remind and advise over the convenience of using condoms to avoid HIV transmission and other sexual transmission diseases. They will be also recommended to be vaccinated against HBV and/or HAV (level C).

HIV and HBV transmission occurs by the same paths. Therefore for the primary prevention of HBV infection in HIV+ patients, all messages and usual strategies for the prevention of HIV infection must be reinforced: measures for the control of sexual transmission risk or parenteral and vertical transmission risk (level C).

There is at least one study suggesting that during the treatment of HIV infection with lamivudine, patients susceptible to HBV infection would be protected against it[99]. However, this strategy has not been specifically evaluated with preventive goals and therefore cannot be recommended (level C). Moreover, in such a situation it is possible to become infected with HBVstrains which are resistant to lamivudine[100].

*Secondary prevention*

Coinfected people by HIV and hepatotropic viruses must be informed about those situations easing the progression of liver damage as the consumption of alcohol or medicines, including herbal products or susbstances used in alternative medicine or illegal drugs (level C).

Some HIV-infecetd patients keep a high alcohol intake, even when they are diagnosed with chronic hepatopathy. In some series, over 30% of them keep an alcohol intake higher than 50 g/day[29,101]. Alcohol, together with HIV and immunodeficiency, is a main cofactor speeding up the progression of HCV chronic hepatopathy. An alcohol intake over 50 g/day increases by 4-fold the risk of developing cirrhosis and anticipates by 10 years the evolution to cirrhosis in patients with chronic hepatitis C. In HCV and HIV coinfected patients with less than 200 lymphocytes CD4+/µl and alcohol intake over 50 g/day, the mean time for the development of cirrhosis is estimated in 16 years since the time of HCV infection. This period increased to 36 years when the lymphocyte count was higher than 200/µl and there was no alcohol consumption[29].

Therefore, in any HIV+ patient with hepatopathy, the consumption of alcohol must be assessed and if it is greater than 20 g/day, it must be recommended the total withdrawal of its consumption, of course evaluating the need (or not) of programmes aimed at supporting the withdrawal (level C).

*Immunizations against hepatotropic viruses in HIV-infected patients*

HIV+ patients may be at risk of suffering some infections that can be prevented by means of vaccines. The problem is the timing election of the vaccination, since the disease progress

can mean an increase of the adverse reactions hence decreasing the vaccine effectivity. In addition to the risk of serious complications from attenuated vaccines, there is the risk that T cells become activated by the vaccination which could increase the viral replication.

*Hepatitis A vaccination.* Most recent recommendation for hepatitis A vaccine in our sitting was made in 1998 by the Public health Commission (table 4). Even though the recommendations included hemophilics, homosexual males and IDUs, none explicit reference to HIV infection is made nor to HCV or HBV chronic infections which, as mentioned, are highly prevalent among HIV-infected patients in Spain.

In patients with chronic HCV or HBV hepatitis, it is highly advisable the hepatitis A vaccination since the risk of fulminant hepatitis associated with the HAV infection can be increased in coinfection situations, though other studies challenge this evidence[69,102]. US organizations of experts as the US Advisory Committee on Immunization Practices (ACIP), the American Liver Foundation, American Digestive Health Foundation and the American Academy of Pediatrics recommend the immunization against HAV in all patients with chronic liver disease (level C).

In the Spanish population the prevalence of antibodies against hepatitis A is high, yet it varies widely according to the age. In people older than 40 years, it is over 90% and in 25 to 30 year-olds the prevalence is about 50%. Most HIV+ patients in our milieu are older than 30 years. Cost-effectivity studies recommend to determine IgG antiHAV before the vaccination when the expected prevalence of antibodies in the target population is over 30%. Thus, in HIV+ adult people it is cost-effective to determine the IgG antibodies against HAV prior to the vaccination indication.

HIV-infected patients respond appropriately to hepatitis a vaccine when they have over 200 lymphocytes CD4+/µl (70% seroconversion rate). On the contrary, the response is very poor when there are less than 200 lymphocytes CD4+ (9%)[67].

It is thus recommended to indicate HAV vaccination in all HIV+ patients who are susceptible (negative IgG HAV) with a count of lymphocytes CD4+ higher than 200 cells/mm$^3$ (level B).

*HBV immunization.* HIV-infected patients have a high risk to develop chronic HBV infection after its first infection and if there is a chronic HBV infection, they are prone to develop ART toxicity[103].

The vaccination of susceptible population is the main prevention measure of hepatitis B in the general population. In Spain there are official recommendations on HBV vaccination that include groups at risk of HIV infection yet not specifically the HIV-infected patient (table 5).

The prevalence of positive markers in our sitting which indicate HBV exposure is 70% in people with IDUs history, 36% in homosexual males and 15% in HIV+ heterosexual people. Thus it is cost-effective to determine the HBV serologic status in HIV-infected patients before the vaccine indication.

A special and common situation in HIV+ patients is to have only a positive anti-HBc marker or «anti-HBc alone» pattern. This pattern can have several above-mentioned meanings (see diagnostic section, interpretation of serum markers). In HIV+ patients with a high revalence of HBV exposure, this pattern must be regarded as a true positive[72-75].

In the general population, the efficacy of the hepatitis B vaccine is high and the determining factor of response is the age. The immunogenic response with the standard HBV vaccine administration regime is decreased in HIV+ patients (by 30%-55%) and it keeps a relationship with the lymphocyte CD4+ count (70% seroconversion in patients > 500 lymphocytes CD4+/µl)[104-108]. The response to HBV vaccine

TABLE 4. **Recommendations for the utilization of the hepatitis A vaccine in Spain**

The Public Health Commision, held on October 29th, 1998 recommended the vaccination against hepatitis A in the following situations:

1. Travellers moving to hepatitis A endemic countries
2. Workers in contact with non-purifed sewage
3. Personnel working in day nurseries
4. Hemophilic patients
5. Homosexual males having multiple sex contacts
6. Intravenous drug addicts
7. Relatives or care-givers having direct contact with hepatitis A patients
8. Medical or paramedical personnel from hospitals and healthcare institutions (including administrate personnel as well as service workers such as cleaners)
9. Personnel involved in catastrophic situation (Police bodies, etc.)
10. Professionals of the Military Forces

TABLE 5. **Hepatitis B vaccination policies in Spain**

In 1982, it was started the vaccination against hepatitis B by means of a selective vaccination of risk groups. In June 1990, the Inter-territorial Council of the National Health System agreed to recommend hepatitis B vaccination in the following population groups:

1. Newborns to carrier mothers
2. People practicing common, mechanically uncontroled cutaneous punctures (IV drug users, etc.)
3. Health and other related personnel having common contact with blood and needles, especially personnel under training
4. Other personnel working in health centers, on the basis of their degree of exposure to potentially infected materials and products
5. Prisoners and prison workers
6. Usual coagulation factors receivers
7. People undergoing multiple transfusions
8. People undergoing hemodialysis
9. People with mental retardation living in institutions and working personnel having contact with them
10. Population frequently changing their partners (homosexuals and heterosexuals)
11. People living at carriers' same home and carriers' sexual contacts
12. Travellers going to live over 6 months in close contact with high endemic areas inhabitants
13. People traveling frequently to high-endemic areas, even for short periods, when it is assumed the possibility of having sexual contacts
14. Special cases and circumstances making it advisable the vaccination

The group of newborns, to carrier mothers, deserves the highest priority among all these groups. Moreover, the vaccination in the group of IV drug users will be encouraged

In 1992, the conference on Vaccinations' Program and Registry (set up thanks to an agreement by the Inter.-territorial Council), agreed to recommend all the Autonomous Communities to develop hepatitis B vaccination programmes in teenagers, according to their possibilities

in immunocompromised patients can increase by 90% with higher doses of antigen and/or increasing the number of inoculations. The standard regime of HBV vaccination is three doses (0, 1 and 6 months) of 20 mcg per dose. Some authors or institutions, as the Atlanta-based CDC, recommend to use the double quantity per dose in HIV+ patients and 4 doses in a 0,1,2 and 6 months scheme (minimal interval between doses)[109]. The experience of the Sandoval Clinic in 70 HIV+ patients vaccinated with 4 doses of 40 mcg (0, 1, 2 and 6 months) showed a seroconversion rate of 84% (anti-HBs > 10 U/l), while the conventional regime in 31 patients showed it to be 64%[108,110].

In immunocompromised patients there will be eventually a greater protection loss than in immunocompetent people[111].

Therefore, it is recommended to vaccinate against HBV all HIV+ patients who are HbsAg and anti-HBc negative as long as they have not been vaccinated previously (level B). In HIV+ patients with the anti-HBc alone pattern, it is not recommended that HBV vaccination (level C). It is prefered the vaccination with 4 doses using double quantity of antigen (level B).

## Antiretroviral treatment in patients with hepatopathy

*ART hepatic toxicity*

Liver toxicity has been reported with the 3 families of drugs used in ART, yet its incidence and pathogenetic mechanism differes between the agents used[103,112,113]. In a retrospective study of over 10,000 patients included in 21 clinical trials of antiretrovirals, it was estimated an overall incidence of hepatotoxicity degree 3/4 due to ARV of 9%, more common with PIs (12%) than with non-analogues (8.5%) or analogues (8%). 23% patients had to stop definitely the ART therapy. 2.5% of overall mortality was attributed to a liver cause. PIs were associated with a greater hepatotoxocity rate but they showed a lower rate of definitive interruption of the treatment and of deaths related to liver abnormalities[114]. Hepatic toxicity associated with ART is more frequent in coinfected HCV or HBV patients although most of these patients will tolerate the treatment without problems[103,112,115-117]. There is therefore not enough evidence to counterindicate any of the ART currently employed in clinical practice in patients coinfected by HIV and by HCV or HBV.

Among the nucleoside analogues, the hepatotoxicity has been more commonly reported with AZT, ddI or d4T in the form of liver enlargement, liver enzymes abnormalities and/or lactic acidosis[118-123]. Abacavir or 3TC have also been involved but at a lesser degree. The involved mechanism is mainly a hepatic mitochondrial toxicity while most common clinical manifestation is a fatty liver disease. It is a relatively common manifestation in patients having the genotype 3 of

HCV[124,125]. Preliminary evidences suggest a greater risk of hepatotoxicity with nucleoside analogues in HCV genotype 3 coinfected patients, which could be related to a greater predisposition to the development of fatty liver disease[126]. The apparition of liver toxicity when administering nucleoside analogues is important given the potential for the development of lactic acidosis. Since nucleoside analogues are a common basis in most ART strategies, in case of subclinical hepatotoxicity (e.g, fatty liver disease without clinical manifestations) their withdrawal will not be recommended and, in any case, it will be considered the convenience of substitution by drugs with less hepatotoxic potential (level C). In patients with symptomatic toxicity, especially hepatopathy associated with symptomatic lactic acidosis, there will be considered the treatment without analogues or with drugs with fewer toxic potential as ABV, 3TC and/or tenofovir (nucleotide analogue) (level C). It is not clear that previous hepatopathies are a risk factor for the development of hepatotoxicity and/or lactic acidosis due to nucleoside analogues, yet it is possible that it can be more symptomatic or serious in patients with hepatocellular insufficiency, so special attention must be paid on patients with cirrhosis requiring ART (level C). The only predisposing factors which are well-recognized, and to bear in mind, are the obese woman or pregnant woman and the prolonged exposure to nucleoside analogues.

In the case of abacair, hepatic toxicity can appear as a hypersensitivity reaction, which happens in 3% of patients at the first month of ABV treatment. In these cases, the treatment must be halted and abacair must not be reintroduced due to the high risk of severe toxicity (level C).

Lamivudine is regarded as the safest nucleoside analogue. Exceptionally it has been associated with liver toxicity due to mitochondrial toxicity. It can be associated with a transient increase of transaminase levels at first weeks of treatement, apparition of HBV resistance (mutation of HBV DNA polymerase) or interruption of 3TC treatment in patients coinfected by HIV and HBV[76-127].

Hepatic toxicity associated with non-analogues of nucleosides develops in 5%-20% of patients[128-130]. It is more common and severe with nevirapine but not exclusively. The toxicity mechanism involves a hypersensitivity reaction. Hepatic toxicity due to non-analogues is more frequent in women129, when there is a coinfection by other hepatotropic viruses[130,131] and possibly in patients with previous hepatic or renal dysfunction[132]. When there is hepatic toxicity associated with treatment with non-analogues , it is recommended to halt and susbstitute them by other antiretroviral agents such as ART of the same family since it has not been demonstrated a crossed reaction between non-analogues regarding liver toxicity nor regarding other hypersensitivity reactions (level C).

Hepatic toxicity in PI treated patients is well known and relatively common. Between 1-30% patients treated with PI will have increases of transaminases (degree III/IV) or will develop a picture of acute hepatitis after starting PI therapy. It has been reported liver toxicity associated with all the agents of this family  yet not all PIs have the same hepatotoxic potential[103,116,133-136]. Ritonavir, administered at ART doses, is significantly more hepatotoxic than the rest of PIs[103]. This alteration is more common in patients coinfected by HCV or HBV, with abuse of alcohol or simultaneously treated with d4T[103,116,137-139]. Unlike the hepatotoxicity associated with non-analogues which turns up during the first weeks of therapy in most cases, that associated with PIs can appear at any time during the treatement. When it is during the first weeks, in coincidence with the immunological improvement and control of HIV viremia, if the patient has a HCV or HBV coinfection, the liver toxicity may owe to a phenomenon of hepatitis by immune reconstruction rather than a direct toxic effect[140]. There have been reported cases in which the picture of liver toxicity has resolved without halting the PI treatment and other cases in which PI therapy has been reintroduced without observing further hepatotoxicity[134]. Despite the common association between hepatotoxicity and PI treatment, almost 90% of HIV+ patients, regardless of whether they are or are not coinfected by hepatotropic viruses, will tolerate adequately the ART treatment with no liver toxicity[103]. It has also been described that ART treatment, and in particular PI, may have a an antifibrotic effect in patients with chronic hepatopathy[30]. Therefore, PIs therapy in patients coinfected by HIV and HCV or HBV is not counterindicated (level B). In any case, it is important to

closely watch over possible hepatotoxicity as a direct effect of the drug or as an effect resulting from the immunological improvement. But to differentiate these two mechanisms is difficult at a clinical practice level.

*Management of ART in patients with hepatopathy*[141]

In patients with hepatopathy, the metabolism and bioavailability of ART can be impaired leading to an increase in the toxicity or alteration of their antiviral activity. The following situations can be considered:

1. *Acute hepatitis*. In HIV+ patients, the development of acute hepatitis is relatively frequent, e.g, hepatitis A, hepatic cytolysis flares in patients with chronic hepatopathies, drug or alcohol toxicity. In thee cases, ART must be withdrawn and reintroduced when the problem has been resolved (level C). Although there are no studies of such situations, it is very likely that the liver dysfunction associated with acute hepatitis pictures impairs the ART metabolism and in turn the hepatic toxicity of these agents may be increased hence making it difficult the resolution of the picture.
2. *Chronic hepatitis without signs of hepatocellular insufficiency*. This situation is very frequent in clinical practice. The ART efficacy is not compromised (there is some controversy such as a fewer immunological recovery, although the probability of reaching a undetectable viremia is not decreased) and a wide clinical expertise indicates that they can be used at the usual doses (level B). There is a greater risk of hepatic toxicity in these circumstances, yet it has not been demonstrated a greater risk of extrahepatic toxicity. In such a situation, nucleoside analogues and efavirenz are safer than nevirapine or PIs.
3. *Chronic hepatopathy with signs of hepatocellular insufficiency*. In patients with cirrhosis or severe hepatic insufficiency, the metabolism of drugs using the P450 cytochrome enzymatic system or the glucuronoconjugation is decreased. However, there are not enough studies so that therapeutic recommendations and dose adjustments can be justified so far.

Among nucleoside analogues, only zidovudine has a high hepatic metabolsim, it is accumulated in case of hepatic insufficiency and thus its dose must be reduced to control its toxicity[142-144] (level C).

In patients with cirrhosis, as mentioned above, there is a greater risk of lactic acidosis (level C).

Among non-analogues, efavirenz can be administered as full doses in patients with liver insufficiency (level C). Its absorption is decreased in such cases and thus balances its lower elimination rate which results in non-significant differences regarding the exposure to the agent (area under the curve)[145]. Nevirapine can be especially toxic in patients with liver insufficiency thus its administration must be avoided if possible[132] (level B).

PIs are drugs with a highly diverse interindividual bioavailability and they are widely metablized in the liver. Thus it is difficult to foresee their bioavailability, and especially in case of liver insufficiency. In such a case, they can be administered adjusting the dose according to the degree of insufficiency (Child-Pugh degree)[146-148]. In these patients, in order to reduce the toxicity and preserve the drug antiviral activity, it is recommended, if possible, to fit the dose by determining the drug levels once the equilibrium state has been attained[149] (level C).

## About the indication of liver biopsy in coinfected patients

*Hepatitis B*

The histologic activity of HBV chronic hepatitis varies from patient to patient and has a close and direct relationship, like the GPT concentration, with the probability of therapeutic reponse to alpha-interferon. The relationship between the necroinflammatory activity at the liver biopsy and the response to lamivudine treatment is less defined, although there is evidence of a higher seroconversion rate in those patients with higher GPT baseline levels. There is a consensus to recommend a liver biopsy in any patient with chronic hepatitis B before starting the immunomodulating or antiviral treatment (level C).

*Hepatitis C*

At a time when the response to antivirals in HCV chronic hepatitis was low and it was not possible to make the diagnosis of active

replication by molecular techniques, liver biopsy constituted a necessity as for therapeutic decision making.

Currently, the efficacy of antiHCV treatments has significantly increased with the combination of interferon and ribavirine. In addition, we can confirm the active viral replication and other causes of hepatopathy can be excluded by means of analytical techniques. However, biopsy remains the only method with the capacity of assessing with reliability the fibrosis and inflamation degree of the liver. We do not know accurately the factors that predict fibrosis development nor the time needed for it to develop; this velocity of development of fibrosis can widely vary from patient to patient. Neither transaminases levels nor HCV viral load nor the genotype are good predictors of the degree of pathology found at the liver biospy.

There has been opened a parallel debate about the convenience or not of performing a liver biopsy in all patients with HCV chronic hepatitis who may be potantial candidates to receive antiviral therapies. Those who oppose a systematic liver biopsy argue its cost, the possibility of serious complications (though these have minimized with recent techniques) and the convenience of an early antiviral treatment, regardless of the degree of liver damage, on the basis of its association with a greater efficacy. It can be argued that the greater the efficacy of the antiviral therapy, the lower the necessity of identifying patients with a higher risk of histologic progression for a therapeutic selection. Arguments backing the performance of a liver biopsy are the possibility of excluding other liver disease causes as well as the aid provided by an accurate diagnosis and prognosis at the time of balancing the advantages and disadvantages of the antiHCV treatment regarding the handling of secondary effects. Many clinicians believe that patients eligible for antiviral treatments are those with the greatest risk of histological progression. Fibrosis extension (presence of portal and periportal fibrosis) is the best marker of risk to develop an advanced hepatic disease. The liver biopsy result can also help establish individual or collective therapeutic strategies in comorbility situations or when there is a limitation of therapeutic resources, respectively.

In the HIV-HCV coinfection, it is important to bear in mind that the antiHCV therapy is not well-defined, the probability of therapeutic response is lower than in monoinfected patients and there may appear a higher number and more severe secondary effects which means that the indication of therapy uses to be more individualized. In these cases, the result of the liver biopsy may be useful in order to decide starting antiHCV treatment (see later). Also, performing a liver biopsy prior to the therapy will help us understand better the future results. But it is also less probable that liver biopsy in coinfected patients reveals a practically non-advanced hepatopathy that could suggest to delay the beginning of treatment.

The consensus of this Working Group regardin the indication of liver biopsy before the beginning of antiHCV treatment in HIV coinfected patients is to recommend it in all cases, except for a formal counterindication. However, the lack of a liver biopsy result must not affect the indication of antiviral therapy in patients with a chronic HCV infection, especially in those patients with highly favourable predictive factors of pre-treatment response, as it is the case of patients infected by HCV genotypes 2 or 3. When a liver biopsy is not available, the antiHCV treatment must be considered according to the remaining treatment indication criteria (sustained increase of transaminases, demonstration of active viral replication and absence of therapeutic counterindications regarding interferon and/or ribavirine) (level C).

## Pharmacologic treatment of chronic viral hepatitis in HIV-infected patients. Evidences and lessons from HIV negative patients and limitations of their extrapolation to the HIV-infected patient. experience in coinfected patients

### Chronic B hepatitis

*Treatment of chronic HBV hepatitis in HIV negative patients*

The primary goal of the treatment of chronic hepatitis B is to permanently suppress viral replication, since this fact is associated with a normalization of transaminases and histologic

improvement involving both necrosis and inflammatory activity. In patients treated with sustained suppression of viral replication, survival increases and decreases the risk of of developing complications such as cirrhosis, hepatocarcinoma or need of liver transplantation[150-152]. The suppression of viral replication is characterized by DNA HBV disappearance from the serum and seroconversion of HBeAg to antiHBe. It is possible to eradicate HBV with antiviral treatment occasionally and this fact will be characterized by the criteria of suppression of HBV replication and conversion of HbsAg to antiHBs. Even in these cases the eradication may not be complete since it has been demonstrated that ther may be cases of reactivation of the replication likely from the viral lathency in hepatocytes or mononuclear cells[153,154].

Treatment for chronic hepatitis B includes alpha-interferon and lamivudine (level A). Other possible treatments or combinations are currently under study and some with potential clinical use such as adefovir.

*Alpha interferon.* Several controlled clinical trials and metaanalysis performed since 1975 have permitted to define the regime, maximum effectiveness and factors predicting the response.

Regimes based on doses higher than 10 MU or treatments longer than 24 weeks do not improve the efficacy but there are more side effects. Doses lower than 5 MU or shorter than 4 months are less efficacious.

With the approved therapeutic scheme of 5 MU/day or 10 MU/3 times a week for 4-6 months, approximately one-third of patients show a negativization of serum DNA HBV with antiHBe seroconversion (therapeutic goal), while this facc only occurs in 8%-10% of controls[155-158].

Out of the patients responding to treatment, about 15% have a relapse with increase of transaminases and markers of active viral replication before one year of the suspension of interferon[159]. The rest of responders keep the response, especially if there is a seroconversion to antiHBs (1/3), which can happen even several years after the treatment. Thus the probability of controlling in a sustained form HBV replication with an associated clinical and histological benefit increases three-fold with interferon treatment with regard to the natural evolution of chronic HBV hepatitis.

Carriers of precore mutation (HBeAg negative) respond worse to alpha-interferon treatment and, especially, it is normal to see a relapse after the suspension of the treatment, even extending the treatment up to 1 or 2 years. Sustained response finally achieved with criteria of suppression of viral replication (undetectable DNA HBV) is only 10%, not very different from the spontaneous response[160,161].

Criteria of treatment with alpha-interferon in patients with chronic hepatitis B are: presence of active viral replication during more than 6 months (HBeAg and/or DNA HBV positives), sustained increase of GPT and liver biopsy with criteria of active chronic hepatitis (level A). Patients with cirrhosis grade B or C of Child must not be treated nor those in which interferon therapy is counterindicated[7,162,163]. Currently in patients with HBeAg negative/anti-HBe positive, it is not considered the treatment with interferon as a first-line therapy as there are other more efficacious alternatives.

The predictive factors of response to therapy with alpha-interferon are: low levels of DNA HBV in serum (< 200 pg/ml by hybridization technique), presence of HBeAg (wild-type), increased levels of GPT and hepatic damage with high necroinflammatory activity. Other factors associated with a better response are: infection acquired in the adulthood, female gender, recent history of disease acquisition, heterosexual behavious, absence of HDV infection, absence of HIV infection or immunosuppression[7,162,163].

*Lamivudine (3Tc).* It is a nucleoside analogue inhibiting HIV inverse transcriptase and the DNA polymerase of the HBV. Unlike interferon, it shows a good tolerance and oral bioavailability.

Lamivudine is a potent inhibitor of HBV replication. At doses of 100 mg/day, it leads to 4 log drops of HBV viremia, attaining a high percentage of maximal suppression of viral replication (undetectable serum DNA HBV). After one year of treatment, the rate of response (GPT normalization and loss of DNA HBV and HBeAg) is higher than 60%, but after withdrawing 3TC the response is only maintained in 17%-20% of patients (permanently negative DNA HBV amd seroconversion to antiHBe). Up to 50% patients have a histologic improvement with 3TC treatment[164-166].

The seroconversion rate to antiHBs is slower than with alpha-interferon.

The rate of reponse (seroconversion to anti-HBe) is higher in patients with higher baseline GPT (5% in patients with GPT < twice the upper limit of the range of normality; 34% if GPT > twice and up to 64% if GPT > 5 times). It is also greater is the treatment with lamivudine is longer. In a study of 58 patients treated up to 4 years with lamivudine, 100 mg/day, seroconversion rate was 22% at one year, 29% at 2 years, 40% at 3 years and 47% at 4 years of treatment[167].

Doses greater than 100 mg/day do not increase the antiviral activity against HBV.

The high rate of relapses after halting the treatment owes to the fact that lamivudine is not able to eradicate cccDNA and, like HIV infection, when the antiviral pressure is stopped, HBV replication reactivates. After the suspension of lamivudine, there can appear an acute flare of hepatonecrosis and even functional hepatic decompensation. Also lamivudine can induce the apparition of HBV resistance, mainly due to mutation of the YMDD domain of the DNA polymerase gene (mutation M552 I/V similar to M184V that confers resistance of HIV inverse transcriptase to lamivudine). After one year of treatment, there is resistance in 15%-30% cases, at 2 years in 40% cases and at 3 years in just over 50% of patients under treatment. It is possible that subtypes adw, less prevalent in our sitting, have a worse response with a greater risk of developing resistance to lamivudine[9,10]. The meaning of the apparition of this mutation with regard to the treatment with lamivudine in chronic hepatitis B is unclear. In those cases with development of mutation and reappearance of HBV active replication, it has been seen that:

1. Prolonged treatment increases the resistance rate but this does not avoid the seroconversion rate to anti-HBe to continue increasing. In the study by Chang et al, 39 out of 58 patients (67%) developed mutation in the YMDD motive. In spite of this, 33% of patients developing resistance had anti-HBe seroconversion[167].
2. Resistant variants replicate with lower affinity than wild-type variant.
3. Viral replication in patients with development of mutation is of lower intensity on the basis of DNA HBV lower levels regarding basal levels and the sustained biochemical remission (normal GPT) in many of them. 59% of 58 patients in the Chang's series kept normal levels of transaminases despite developing lamivudine resistance[167]. In other patients, the reapparition of viral replication is accompanied with necroinflammatory acute activity and even decompensation of the chronic hepatopathy.
4. If treatment with lamivudide is suspended in those patients who have developed resistance due to mutation of the DNA polymerase gene, such a mutation reverses after 3-4 months in coincidence with an increase in the viral replication activity.

Lamivudine is efficacious in patients with negative predictive factors of response to alpha-interferon treatment, including patients infected by precore mutant (HBeAg-/anti-HBe+) and immunocompromised. Response to lamivudine in those patients with chronic HBV anti-HBe+ hepatitis is similar to that of patients HBeAg+ (65% of responses at one year of therapy and 17%-24% after one year of therapy, with 27% of resistant variants at one year of therapy). Failure of previous therapy with alpha-interferon does not predict a failure of lamivudine therapy.

In summary, lamivudine therapy in patients with chronic hepatitis B is as afficacious but less toxic than the treatment with alpha-interferon and its efficacy is not affected by negative predictive factors (level B). For that reason, many clinicians use lamivudine as a choice treatment in chronic B hepatitis and raise the possibility of interferon as a first-line therapy only in those cases with prognostic factors of highly favourable responses. Lamivudine is recommended at a dose of 100 mg/day during one year at least. Many authors think that the treatment must be maintained up to 2 months after antiHBe seroconversion and that, even in case of developing resistances, the treatment must be kept to avoid a reactivation associated with its interruption and thus the velocity of progression of the hepatic disease decreases (level C).

*Other treatments:*

1. *Combined therapy with interferon and lamivudine.* Data from a randomized clinical trial with 230 patients showed a greater rate

of conversion in the combined therapy arm (29%) versus treatment with alpha-interferon (19%) or lamivudine (18%) which did not reach statistical significance. However, it is possible that different regimes associating interferon with lamivudine lead to better results.

In a pilot study, 14 patients who were resistant to alpha-interferon were sequentially treated with 3TC (20 weeks), alpha-interferon and 3TC (4 weeks) and finally alpha-interferon alone (24 weeks). Eight patients had undetectable serum DNA HBV 6 months after stopping the treatment, 5 showed a seroconversion from HBeAg to anti-HBe and three from HbsAg to anti-HBs[168]. In another study, the treatment with interferon was compared with lamivudine therapy and with interferon and lamivudine treatment in patients who did not respond to a first cycle of interferon. The group retreated with interferon had rates of HBeAg negativization of 13% and of transaminases normalization of 15%, while in those treated with lamivudine or with lamivudine plus interferon these rates were 33% and 44% and 21% and 18%, respectively.

The efficacy of the combination of alpha-interferon and lamivudine vs sequential monotherapy with both agents has not been previously studied in comparative trials in previously untreated patients.

Therefore, on the basis of these results, it is not currently recommended the combination therapy as the starting therapy in chronic HBV hepatitis nor as rescue therapy when there is a failure of the therapy with alpha-interferon.

2. *Famciclovir*. At doses of 500 mg/8 h during 12 months, it is efficacious in the treatment of chronic hepatitis B according to histological and virological criteria, but the rate of seroconversion to antiHBe (9% vs 3% in the placebo group) is lower than with lamivudine.

3. *Emtricitabine (FTC)*. In one study in chronic hepatitis B, after two months of treatment, 50-87% patients had undetectable serum DNA HBV. FTC generates the same type of resistance as lamivudine[169].

4. *Adefovir*. It is an inhibitor both of HIV and HBV replication. At the required dose to effectively inhibit HIV replication, it is a nephrotoxic agent and, as a result, its development as an antiretroviral agent has been halted. At doses of 10-30 mg/day is well tolerated, attaining seroconversion responses similar to 3TC (22%), is effective in the treatment of infections by HBeAg+ or HBeAg- or lamivudine resistant strains and does not induce resistance easily[170-172]. It is an alternative to bear in mind nowadays as a treatment of chronic HBV infection both in previously untreated patients and in lamivudine resistant patients.

5. *Entecavir*. It is active against hepadnavirus including lamivudine resistant strains and it represents a drug to bear in mind for the near future.

6. *Pegylated interferon*. It is potentially more effective than alpha-interferon, yet studies are still on a developmental stage and specific recommendations for its use in chronic hepatitis B cannot be made as yet.

In summary, the current treatment of chronic hepatitis B is based on the therapy with lamivudine and, in selected cases, with alpha-interferon (level A). Adefovir can be used with the same objective (level B). There are expected results from ongoing studies with new nucleoside analogues, combined therapy with antivirals and/or immunomoduling agents as well as therapeutic vaccines combined with antivirals and genetic therapy.

*Treatment of chronic hepatitis B in HIV-infected patients*

The extrapolation from the results of the studies of the therapy of HBV infection in HIV negative patients to HIV-coinfected patients has become difficult due to the following factors:

1. The natural history of HBV infection is different in coinfected patients.
2. Some anti-HIV treatments have anti-HBV activity.
3. The response to immunomodulators can be different in coinfected patients according to the immunosuppression degree.

Therefore, there is the need of performing studies about the treatment of chronic hepatitis B specifically in HIV-infected patients. To date, the experience is very scarce and only limited to pilot studies. Rather than recommendations, it is possible to provide considerations extrapolated from the lessons learned in patients without HIV coinfection.

*Alpha-interferon.* Preliminary conclusions to be drawn on the studies of treatment with alpha-interferon in patients with chronic HBV hepatitis who are HIV+[173-180] are:

1. Heterogeneity of treated patients.
2. Lower efficacy than in HIV negative patients 8undetectable DNA HBV 27%-37% vs 17% without treatment. Less than 10% reach undetectable DNA in a sustained form as well as seroconversion from HBeAg to antiHBe).
3. It is not known if regimes of alpha-interferon other than those indicated in HIV negative patients could increase the efficacy rates until similar figures.
4. The response keeps direct relation with the count of lymphocytes CD4+ at the beginning of treatment and, like HIV negatives, with the basal level of GPT and DNA HBV.
5. Follow-up periods are short and studies are mainly incontrolled so it is not known the long-term efficacy and the impact on the survival or development of cirrhosis or its complications, including hepatocarcinoma and transplantation need.
6. Usual doses employed for the treatment with alpha-interferon in chronic hepatitis B are not well tolerated in general in HIV-infected patients.

*Lamivudine.* The experience of treating chronic hepatitis B with 3TC in HIV+ subjects is mainly based on those patients receiving treatment with lamivudine for HIV infection and thus greater doses (300 mg/day) than those needed for the control of HBV replication[77,127,181-188]. In non-coinfected patients, such a dose has the same efficacy than the 100 mg/day dose.

From the results of these experiences, it can be concluded that:

1. Serum DNA HBV decreases in 99.8% treated patients[181].
2. The response (undetectable DNA HBV) at the beginning of treatment is high but unsustained: 86%-100% at 2-4 months, 25%-47% at 18-24 months, 9% at 48 months[182-186]. The rate of seroconversion to antiHBe uses to be lower than that in HIV negative patients (yet comparative studies have not been performed), although in any case greater than that seen with alpha-interferon.
3. The resistance rate is 20% every year, similar to that observed in HIV negative patients[188]. After 5 years of treatment with lamivudine, almost 100% of patients coinfected by HBV and HIV have developed resistance mutations in the HBV polymerase gene.
4. The development of resistances owes to mutations in the YMDD region of the HBV DNA polymerase gene (M550V associated with L526M, or M550I), similar to immunocompetent patients.
5. Recurrence is frequent after withdrawing the treatment or developing resistances[77,186,187].
6. Patients with resistance mutations to 3TC have lower levels of viremia indicating an attenuation of HBV virulence, although the potential clinical benefit from this fact is unknown.
7. The response to 3TC treatment does not have relation with age, gender, CD4 levels, HIV control nor CDC stage.

*Other treatments.* There is some preliminary experience with some new treatments in HIV+/HBV+ patients.

With regard to FTC, there is a double-blind study using 3 doses (25,100 and 200 mg) in 98 patients. With the 200 mg/day dose, 64% of them reached an undetectable DNA HBV at 36 weeks of treatment[189]. Like patients without HIV infection, the efficacy of FTC seems similar to that of 3TC and has the same resistance problems.

With regard to adefovir, a study of 20 patients on I/II phase was performed. The used dose was 125 mg/day (15 patients) vs placebo (5 patients) for 4 weeks. It was seen a significant decrease of the HBV viremia with a rebound after removing the therapy. The suppression of HBV replication in a coinfected patient treated with adefovir and abacavir indicated the possibility of using adefovir as a rescue in patients with chronic hepatitis B who were resistant to 3TC[190]. Renal toxicity due to adefovir prevents it from being used at efficaccious doses for attaining a control of HIV replication. Yet lower doses, 10 mg/day, are effective for controlling the HBV replication. In a pilot study in 35 patients coinfected by HBV and HIV who were resistant to 3TC (detectable DNA HBV and DNA polymerase M550V or M550I mutation) who were treated with adefovir 10 mg/day for 48 weeks, there

was a 4.27 log decrease of DNA HBV at the week 32 of treatment with 3 seroconversion cases[191]. Recently, such a study has been extended to week 72 and it has been reported a mean decrease of HBV viremia of 4.77 log, in addition to an histological improvement in 14 patients who underwent a liver biopsy again and, interestingly, the non-development of HBV or HIV resistances to adefovir[192]. It has been reported that adefovir at a dose of 10 mg/day in HIV-coinfected patients without sufficient control of HIV replication did not induce mutations at the codon 65 or 70 nor at other sites of the inverse transcriptase gene. But these results must be regarded as preliminary[193]. Therefore adefovir is a potential alternative to be taken into account in the treatment of HBV infection in HIV-coinfected patients.

In 2 pilot studies with 10 and 14 patients, tenofovir, at a dose of 300 mg/day, was effective to reduce the plasmatic HBV viremia in patients displaying a positive DNA HBV after a treatment with 3TC. The mean viremia drop was 4.6 log at the week 24. In this period, development of resistances was not reported[194,195].

There are no comparative randomized studies between different treatment regimes for chronic HBV hepatitis in HIV+ patients nor experiences with combined treatments.

Therefore, in the management of HBV-HIV coinfected patients, the following considerations must be taken into account at the time of individualizing the treatment (level C):

1. To avoid if possible the 3TC and tenofavir monotherapy in patients without ART treatment indication. If it is regarded as necessary to treat the infection by HBV in this situation, we must consider the treatment with alpha-interferon if the patient has favourable response criteria or with adefovir at dose of 10 mg/day (fewer probability of ART compromise in the future regarding the utilization of 3TC or tenofavir).
2. In patients starting ART with no indication for treating HBV infection, it is recommended to avoid, if there are reasonable alternatives, the indication of 3TC and tenofavir not to compromise future options of antiHBV treatments such as, for instance, combined antiviral treatments.
3. If it is actually indicated starting ART therapy and it is regarded as necessary the control of HBV replication, 3TC must be included in the scheme. Tenofovir can be considered also in the future.
4. In patients with HIV and HBV sensitivity to 3TC, if such agent is indicated, it is recommended to use always a dose of 300 mg/day within an ART scheme.
5. If the infection by HBV is resistant to 3TC but this is not the case of HIV infection, 3TC treatment will be maintained at a dose of 300 mg/day in order to ensure an antiHIV activity as well as the benefit associated with a decrease of the HBV replicative capacity. In such situation, it can be considered to add tenofovir at a dose of 300 mg/day (with or without lamivudine substitution) or to add adefovir at a dose of 10 mg/day.
6. If HIV infection is resistant to 3TC but this is not the case of HBV infection, the dose of 3TC can be reduced down to 100 mg/day in combination with the HIV rescue scheme. If in the HIV rescue scheme tenofovir is included, then it can be considered to keep the treatement with 3TC or halt it.
7. If 3TC treatment is suspended in a patient with chronic HBV infection (e.g, resistance, toxicity, interruption for ART change) without including another agent with antiHBV activity (tenofovir, adefovir), it is recommended to closely watch over the development of a hepatonecrosis flare.
8. The benefit of antiviral therapy has not been sufficiently demonstrated in patients with advanced HBV chronic hepatitis. Some of these patients might be liable to liver transplantation in the future. In this setting, the initiation of antiviral therapy for HBV infection on the one hand, and the possibility of reserving drugs active against HBV to use them in the pretransplant phase in order to minimize the risk of HBV graft infection on the other hand, must be weighed.

## Chonic hepatitis C

*Chronic hepatitis C therapy in patients without coinfection*

Since 1998 the standard treatment for chronic hepatitis C is the combination of interferon alpha plus ribavarine with regard to a greater efficacy than interferon monotherapy.

This treatment has confirmed the same therapeutic principles and predictive factors of response which had been defined in the interferon alpha monotherapy era. The development of pegylated interferons, with a more adequate bioavailability than conventional interferon alpha has allowed the development of even more effective combination therapies and also the possibility of predicting response from the changes observed in viral load during the first weeks of treatment.

*Anti-HCV treatment endpoints.* The primary endpoint of antiviral therapy for chronic hepatitis C is HCV eradication. Eradication is considered to be highly likely if HCV replicative activity is not detected after 6 months of the end of therapy (sustained response). This situation correlates with a high probability of hepatic biochemical and histological improvement and a decrease of the risk of developing liver cirrhosis and associated complications, including hepatocellular carcinoma and death due to liver causes in the long term. Aminotransferases normalization and HCV viral load at the end of therapy (response at the end of therapy) are secondary efficacy markers. The modification in viral load after the start of therapy has a certain predictive value for response, depending on the moment of determination and the therapy regimen. If HCV determination in plasma is positive after six months of therapy the probability of increasing the sustained response rate maintaining treatment for one year is minimal, on account of which it is advised to discontinue it. Recently, interest has raised over qualitative and quantitative changes in HCV viremia at the first and third month of therapy compared with baseline viremia as predictors of response at the end of therapy, especially in order to evaluate lack of response[90-92].

The improvement in hepatic histology, even in patients without a complete eradication of viral replication, is recommended as a therapeutic endpoint. A recent review of 3,010 patients included in 4 clinicl trials treated with diverse interferon alpha 2b or pegynterferon alpha 2b (12 kDa) regimens, with or without ribavirine, and who had a liver biopsy prior and after treatment (with a median time of 20 months between biopsies), showed an improvement in the necroinflammatory activity with all regimens. This was clearly superior with the pegyinterferon alpha 2b (12 kDa) plus ribavirine combination (73%), with the interferon alpha 2b without ribavirine showing an inferior efficacy (39%). Histological improvement in multivariate analysis is particularly associated with a sustained virological response after the end of treatment, but it also occurs in nonresponders. An important result from this study, and previously not recognized, was the regression of cirrhosis (fibrosis $< 4$) observed in 49% of 153 patients who had a cirrhosis at entry, which was particularly associated with HCV viral replication elimination[196]. This fact could explain the improvement observed in morbidity and mortality of these patients, although this has not been demonstrated yet[197].

*Regimens of antiviral therapy for chronic hepatitis C.* Three randomized, double-blind clinical trials showed an undoubtedly superior efficacy without an excessive increase in adverse events of the combination of conventional interferon alpha and ribavirine versus conventional interferon alpha monotherapy, both as initial treatment or as rescue therapy[198-200]. In consensus meetings in America and Europe it was concluded that the standard therapy for chronic hepatitis C, in the absence of contraindication for the use of ribavirine, was the combination of conventional interferon alpha, 3 MU three times per week, plus ribavirine, 1000-1200 mg/day, for 24-48 weeks (level A).

The addition of polyethylene glycol molecules to conventional interferon alpha gives rise to a new molecule, pegyinterferon or pegylated interferon, more soluble in water and with a different metabolism, and therefore with a significant prolongation of its half life. Due to these changes, pegylated interferon can be administered once per week, and, with respect to conventional interferon alpha, has an improved bioavailability (maintained plasma levels and increase of area under the curve). There are two types of pegylated interferons, the one derived from interferon alpha 2a (40 kDa) (PEGASYS) and the one derived from interferon alpha 2b (12 kDa) (PEG INTRON), showing differences in the method of pegylation, and therefore in their metabolism and bioavailability. To the date, pegynterferon alpha 2b (12 kDa) is commercially available in Spain, although interferon alpha-2a (40 kDa) will ve available in a few

months. interferon alpha-2b (12 kDa) is administered in individualized dose according to patient´s weight (1.5 µg/kg/week). Pegynterferon alpha-2a (40 kDa) is administered at a fixed 180 µg/week dose. There are no comparative studies on the use of the different types of pegylated interferon indicating equivalence or differences on the efficacy of each one.

Both pegylated interferon alpha 2a (40 kDa) as 2b (12 kDa) have been shown in clinical trials to be more effective than their corresponding conventional interfenon alpha[201-203].

Recently, two randomized, partly-blind clinical trials have shown that, overall, treatment with pegylated interferon alpha 2b (12 kDa) or 2a (40 kDa) and ribavirine is more effective and equally tolerated than treatment with conventional interferon alpha and ribavirine[204,205]. All patients from both studies were treated for 48 weeks. In both studies the sustained response was significantly better in patients with the genotype 1 treated with the pegylated interferon alpha and ribavirine combination, while the pegylated interferon alpha and ribavirine regimen was superior in patients with genotype 2 or 3 in one study and both regimens showed similar efficacy in the other[205]. Although the use of pegylated interferon alpha 2b (12 kDa) plus ribavirine showed an overall equivalent efficacy than conventional interferon alpha 2a (40 kDa) in patients with genotype 2 and 3, when only the patients who received a ribavirine dose higher than 10.6 mg/kg/day a greater efficacy of pegylated alpha 2b (12 kDa) was demonstrated[204]. Because of their design these studies did not allow to define whether shorter courses of treatment with pegylated interferon and ribavirine (six months) were as effective as one-year courses in all patients or in a subset of patients (e.g., genotypes with more favorable response), Also, the number of patients included with genotypes 4, 5 or 6 was not large enough to analyze these subgroups, although, generally, the response rate and the behavior of the different regimens tended to be similar to the observed in patients with genotype 1. An unplanned analysis of the results of the Manns' study allowed to define a statistically significant association between efficacy and treatment with ribavirine at a dose higher than 10,6 mg/kg/day in all situations, bur especially in patients with a poore probability of response (genotype 1, bridge fibrosis or cirrhosis). In relation with this results, the European Drug Agency recommends the treatment with ribavirine adjusting for weight (800 mg/d if < 65 kg, 1,000 mg/d if 65-85 kg, and 1200 mg/d if > 85 kg). In a recently reported the duration of treatment with pegylated interferon 2 A (40 kDa) plus ribavirine and the more adequate ribavirine dose has been prospectively studieds. Patients with the genotype 1 showed a better response with 48-week courses than with 24-week courses and with weight-adjusted ribavirine 1,000-1,200 mg/day than with a fixed 800 mg/day dose irrespective of weight. Conversely, patients having a non-1 genotype (particularly 2 and 3) did not benefit from a treatment longer than six months nor from a ribavirine dose greater than 800 mg/day[206].

Table 6 shows the probability of achieving response to treatment for chronic hepatitis C in patients monoinfected with HCV, obtained from analyzing jointly the results from the intention-to-treat populations of the main studies. The overall probability will widely very according to genotype distribution in the treated population so it is more practical to take into account the probability of response of each genotype.

TABLE 6. **Probability of virologic sustained response to HCV treatment in monoinfected patients (intention-to-treat)**

| Regime | Mean overall response (range) | Mean response of genotypes 1 (range) | Mean response of genotypes 2,3 (range) |
|---|---|---|---|
| Alpha-interferon, conventional, 12 months | 16% (13%-19% | 9% (7%-11%) | 31% (29%-33%) |
| Alpha-interferon, pegylated, 12 monts | 29% | 21% | 45% |
| Alpha-interferon, conventional + ribavirine, 6 months | 33% (25%-37%) | 17% (16%-18%) | 66% (64%-69%) |
| Alpha-interferon, conventional + ribavirine, 12 monts | 44 % (38%-47%) | 33% (28%-37%) | 68% (61%-79%) |
| Alpha-interferon, pegylated + ribavirine, 6 months | – | 41% | 78% |
| Alpha-interferon, pegylated + ribavirine, 12 months | 56% (54%-58%) | 46% (42%-48%) | 78% (75%-78%) |

As with other antiviral treatments, treatment compliance has been shown to be a critical factor in the efficacy of response in all the settings, especially in those patients with a lesser probability of response. In a study using pegylated inetrferon alpha 2b (12 kDa) plus ribavirine, the patients receiving more than 80% the prescribed dose showed the higher sustained response rate (72% vs 46% of the rest of patients)[207].

In summary, the current therapy of patients with chronic hepatitis C should be pegylated interferon alpha plus ribavirine for a year in patients with genotype 1 (and probably for genotype 4) and pegylated interferon alpha plus ribavirine for 6 months in patients with genotypes 2 or 3 (level A). Although patients with genotype 2 or 3 could be treated with interferon alpha and ribavirine for 6 months taking into account cost/efficacy ratio, the more convenient and adequate administration of pegylated interferon plus ribavirine without an increase in adverse events, and the greater efficacy of this regimen reported in at least one clinical trial, makes advisable the use of interferon alpha and ribavirine as a second choice in this subset of patients (level A). At least in patients with genotype 1, the administered dose of prescribed ribavirine must be higher than 10.6 mg/kg (1,000-1,200 mg, weight-adjusted) (level A). Treatment compliance, both in time and dose, is a factor related to efficacy; so, dose adjustments and treatment interruptions in relation to adverse events are only indicated when necessary or there are no alternatives (level B). Patients showing intolerance, or those in which ribavirine is contraindicated, should be treated with pegylated interferon monotherapy for a year (level A).

*Response-predicting factors.* There are some factors found previously to treatment which are associated with a different probability of response to antiviral treatment in HCV infection[208]. To this effect, the main factors relating a favorable response have been well established and are genotypes 2 or 3, a low HCV viral load, and liver histology showing mild to moderate chronic hepatitis and absence of cirrhosis. Other favorable factors also associated with response to treatment, but not so important, are younger age (less than 40 years-old), history of intravenous drug abuse (probably because a higher prevalence of genotype 3), a shorter time elapsed from HCV infection, and low serum or hepatic tissue iron[198,199]. It is estimated that genotype and viral load account for 80% of treatment response variability, while the rest of factors, namely age, sex and fibrosis stage would account for 20% of such variability[209]. On the other hand, factors predicting a low response rate are, especially, genotype 1 or histologically advanced liver disease. An additional factor associated with a lesser probability of response is the coexistence of immunosuppression. Many of these factors (genotype, high viral load, time from primoinfection, and probably some others) might be related to a greater diversity of the infecting *quasispecies*, and this might be the primary factor in resistance to antiviral therapy, although this fact has not been sufficiently studied[210].

Nevertheless, no pretreatment factor on its own has a negative or positive predicting value for response that it may be considered as an absolute criterion in order to treat or not a certain patient.

The pretreatment factors predictive of response may help to establish the more adequate antiviral treatment for chronic hepatitis C. In a recent substudy based on the clinical trials of interferon plus ribavirine including 1,744 patients, the combination of 5 pretreatment factors favorably associated with sustained response (age younger than 40 years, female, HCV viral load less than 3.5 million copies/ml, absent or minimal fibrosis, F0 or F1, on liver biopsy and genotype 2 or 3) was evaluated. Patients with 4 or 5 favorable factors showed a high probability of response, greater than 50% and there were no significant differences taking into account if treatment duration was 6 or 12 months. Those having less than 4 pretreatment factors predictive of favorable response showed a higher response rate with the 12-month regimens[211]. For this reason, authors recommend to prolong treatment duration to 12 months in patients less than 4 pretreatment factors predictive of favorable response if HCV viral load at week 24 is negative (evidence B). As randomization of patients was not stratified for predictive factors of response in these studies, the results from this substudy should be considered as preliminary and confirmation must be sought.

Once treatment is initiated, it may be useful to monitor HCV viral load in order to pre-

dict final response. To this effect, the absence of virologic response at week 24 predicts treatment failure even though treatment is prolonged until week 48 (2% sustained response vs 3% in patients treated for 24 weeks. On the contrary, a negative HCV viral load at week 24 of treatment is associated with a 74% of sustained response[198,199]. These factors have a positive predictive power that the pretreatment factors mentioned above.

Recently, it has been demonstrated in clinical trials treating patients with pegylated or conventional interferon that a decrease in viral load inferior to 1 log at week 4 or HCV PCR positive showing a decrease inferior to 2 log at week 12 of treatment has a high negative predictive value (> 95%) of final response[90-92, 205]. Even the determination of HCV viral load after an interferon dose might identify patients with primary resistance to treatment and high probability of no response[212,213]. Taking into consideration these criteria, once validated, will allow a lesser exposure of non responding patients to adverse events derived from treatment and also a better cost/benefit ratio. However, it is very important to consider the variability interassay and interlaboratory of the quantitative determination of HCV viral load measured by molecular biology techniques because, as mentioned in the diagnostic section; a difference of up to 1 log may be found between two determinations of the same sample (± 0.5 log).

*Indication for the treatment of chronic hepatitis C.* The indications for the antiviral treatment of chronic hepatitis C have not substantially changed from the ones established in the studies with interferon monotherapy[214]. Treatment must be recommended to patients with a persistent elevation of aminotransferases, positive plasma virus determination, and findings of fibrosis and/or moderate inflammation on liver biopsy (including Child's grade A cirrhosis) and without contraindications to treatment (level A).

*Contraindications for the treatment of chronic hepatitis C.* Among the absolute contraindications for the initiating the treatment for chronic hepatitis C are active drug or alcohol addiction, pregnancy, serious psychiatric disorders, like psychosis, suicide ideas, cardiovascular disease, renal insufficiency with creatinine clearance inferior to 50 ml/min, and unstable liver cirrhosis (Child's grade B or C) 209, VIH infection should not be considered an absolute contraindication for the treatment of chronic hepatitis C[209] (level C).

*Chronic hepatitis C and special situations*

There are some settings in which the antiviral therapy for HCV infection are not well established. In these cases it is recommendable to plan treatment only in the setting of clinical trials or exceptional circumstances. Examples of these situations are chronic hepatitis with mild histological disease, chronic infection by HCV with persistently normal aminotransferases, chronic infection by HCV with extrahepatic manifestations and HBV coinfection.

*Chronic infection C treatment in coinfected patients*

*General considerations.* The evolution of hepatitis C in HIV-coinfected patients is more severe, developing cirrhosis more rapidly. Taking this into account, and as HIV patients will receive potentially hepatotoxic antiretroviral drugs, and that hepatitis C may reactivate after restoring the immune system[140], the indication for the treatment of this hepatic condition might be even more justified than in other patients with out comorbidity (level C). On the contrary, an inferior experience and probability of response due to immunodeficiency or factors associated to poorer response, are more likely in a population coinfected with HIV (greater HCV viral load, unfavorable genotypes, male, comorbidity, etc.) so that clinicians managing coinfected patients might be more reticent to the indication of antiviral treatment for chronic hepatitis C.

Although there are several ongoing studies, we do not have available comparative, controlled, double-blind studies defining with highest efficacy criteria the different regimens of treatment for chronic hepatitis C in patients coinfected with HIV.

The primary endpoint of antiviral therapy for chronic hepatitis C in HIV-coinfected patients should be, as in no coinfected patients, HCV infection eradication (level C). Secondary endpoints of chronic hepatitis C therapy in coinfected patients may be to improve the control and prognosis of HIV infection by improving the safety of antiretroviral therapy in patients eradicating or controlling HCV infection. Preliminary studies have observed a

decrease in HIV viral load ranging 0.5-1.25 during the first 28 days of treatment with interferon alpha or pegylated interferon not attributable to antiretroviral therapy[215].

Also, and although results are still preliminary, it is possible that therapy has beneficial effects in histology, even in patients without virologic response. In the ACTG A5071 study, a histological improvement was found in biopsies performed at 6 months of treatment in 26% of nonresponder patients to pegylated interferon alpha 2a (40 kDa = and ribavirine and in 40% of nonresponders[216].

In order to evaluate treatment for hepatic disease and eventually to establish priorities with respect to antiviral therapy against HCV in a HIV-positive patient, it must be taken into account:

1. Situation with respect to HIV: the consensus panel of experts on chronic hepatitis C therapy of the American National Health Institute recommends that the HIV infection should be under control, the patient has a good clinical and functional situation, and the antiretroviral regimen is stable when considering to treat chronic hepatitis C in a patient coinfected by HIV214. Although viral load is the best marker of HIV infection control, it is truly with the immunologic situation that evidences exist of association with treatment response. The better is the patient´s immunologic situation, the more effective the treatment[217-219].
2. Situation with respect to HCV: the same criteria for the indication of therapy in patients without coinfection must be met, including the recommendation and evaluation of liver biopsy.
3. We must be sure and insist, even stronger than in any other group of patients, on the absolute abstention from drug abuse, especially alcohol, heroine and cocaine, and also consider if the patients is taking any other drugs.
4. No contraindications to antiviral therapy of HCV infection should exist. To this effect, special emphasis should be made on ruling out the coexistence of psychiatric disorders, like depression or suicidal ideas, and also assess the severity and control of hematologic disorders (anemia, neutropenia, thrombocytopenia) which are highly prevalent among HIV-infected patients.
5. We must have in mind and monitor any possible interactions between antiretroviral therapy and the treatment for chronic hepatitis C, especially in a time when the evidences and clinical relevance of theses interactions are still poorly established.

*Experiences on the treatment of chronic hepatitis C in HIV-coinfected patients:*

1. *Efficacy of interferon alpha monotherapy*. Most studies are retrospective, unpublished series of case reports with few patients and with a poor definition of outcome variables or the assessing system (intention-to-treat or per-protocol) and with an insufficient definition of concomitant therapy, especially antiretroviral treatment. In a metaanalysis from these experiences the mean sustained virological and biological response rate ranged between 15% and 19%, respectively, with better results when only cases treated for 12 months were considered (table 7). However, the range of responses was very wide (0%-44%)[218, 220-224].

Other common features of most studies are the inclusion of patients with a relatively good immunological status, generally over 200 CD4 lymphocytes/µl, and also that they had been carried out in a time previous to the establishment of high efficacy antiretroviral therapy. The most reliable published experience comes from the Spanish Group for the Study of Hepatitis-HIV Coinfection[217]. In this prospective study 80 coinfected patients and 27 patients without coinfection were treated with interferon alpha 2b for 12 months. The sustained virological and biological response rate was 22.5% in the coinfected and 26% in the no coinfected patients, a rate similar to the previously described in patients with in the previous literature chronic hepatitis C without coinfection treated with interferon alpha. Other additional findings of this study was that response rate was higher in females, patients with less viral load, and especially in patients with more than 500 CD4+ lymphocytes/µl, which was confirmed in a recent study[218].

2. *Efficacy of interferon alpha plus ribavirine combination therapy*. Experience on interferon alpha plus ribavirine in HIV and HCV coinfected patients is still scarce and is limited to series of case reports. In table 8 there is a summary of series analyzing sus-

TABLE 7. **Sustained response (SR) to interferon treatment in HIV+**

| Source | No | CD4 | SR (IT) | Regime |
|---|---|---|---|---|
| Marriott, et al[224] | 13 | | 4/14 (GPT) | 9 MU/day, 3 months |
| | (1 cirr) | 584 ± 283 | 5/14 (RNA) | 6 MU/day, 3 months |
| | | | | 3 MU, 3/week, 3 months |
| Boyer, et al[220] | 12 | 352 ± 257 | 1/12 (GPT) | 1-5 MU 3/week, 4-6 months |
| | (2 cirr) | (7,200-350) | | |
| | | (2 < 200) | | |
| Mauss, et al[218] | 17 | 525 (resp) | 5/17 (GTP and RNA) | 5 MU, 3/week ≥ 4 months |
| | | 245 (no resp) | | |
| | | (n = 8 and 9) | | |
| Boldorini, et al[248] | 12 | | 4/12 (GTP) | 12 months |
| | | | 1/12 (RNA) | |
| | | | (18 m) | |
| Pizarro, et al[249] | 8 | 400-757 | 2/8 (GTP) | 6 MU, 3/week, 3 months |
| | | | (22 and 48 m) | 3 MU, 3/week, 3 non-responders: a further 6 months |
| Soriano, et al[217] | 80 | > 200 | 18/80 (GTP and RNA) | 5 MU, 3/week, 3 months |
| | | | | 3 MU, 3/week, 9 months |
| Paesa, et al[250] | 17 | 536 ± 241 | 2/17 (RNA) | Differents doses, 6-12 months |
| Linares, et al[251] | 17 | | 5/11 GPT | 3 MU 3/week, 9 months |
| | (data from 11) | | 2/11 RNA | |
| Pol, et al[252] | 16 | | 0/16 (GTP) | 3 MU 3/week, 6 months |
| Marcellín, et al[223] | 20 | 350 | 3/20 (GPT) | 3 MU, 3/week, 6 months |
| De Sanctis, et al[253] | 27 | | 1/27 at two years | 3 MU, 3/week, 18 months |
| Uberti, et al[255] | 27 | > 200 | 1/27 at two years | 6 MU, 3/week, 6 months |
| Stoll, et al[254] | 20 | 342 ± 202 | 0/20 (RNA) | 6 MU, 3/week, 9-12 months |
| Martínez, et al[255] | 14 | > 450 | 2/14 (RNA) | 3 MU, 3/day, 1 year |
| Hayashi, et al [256] | 7 | «low» | 0/7 (RNA) | 9 MU/day, 2 week |
| | | | | 9 MU 3/week, 22 weeks |
| Causse, et al[257] | 63 | | 7/63 (GPT) | 3 MU 3/week, 6 months |
| Prestileo, et al[258] | 41 | | 1/41 | 3-6 MU 3/week, 24 weeks |
| Soriano, et al[259] | 29 | | 7/29 (GPT and RNA) | 5-8 MU 3/week, dose increases |
| Sulkowski, et al[260] | 14 | 343 | 1/14 RNA | |
| Bruno, et al[261] | 50 | 515 | 0/50 RNA | 3 MU/day, 48 weeks |
| Di Martino, et al[262] | 32 | 482 | 2/32 (GTP) | 3 MU 3/week, 24 weeks |
| Total | 535 | | 67/346 GPT (19.3%) | |
| | | | 44/297 RNA (14.8%) | |

SR: sustained response; IT: intention-to-treat.

tained virological response and that included patients without previous hepatitis treatment experience, and in the case of those studies reported in congresses and later published, only the published data have been taken into account.

Overall treatment efficacy with conventional interferon alpha and ribavirine in coinfected patients is around 22% (16%-40%). Some of the series included a high percentage of patients with liver cirrhosis o treatment was limited to six months irrespective of genotype, which could contribute to an inferior response rate than expected when considering the response reported in HCV monoinfected patients. However, some data support that treatment response to hepatitis C with conventional interferon alpha plus ribavirine in coinfected patients is inferior to the observed in HCV monoinfected patients:

- Treatment withdrawal rate due to patient´s refusal or adverse events was higher in coinfected patients (see further on).
- Preliminary results from several randomized clinical trials including a significant number of patients not previously enrolled suggest a low virological response rate early or at the end of therapy with the conventional regimen of interferon alpha every other day and ribavirine for 48 weeks, although in a diffe-

TABLE 8. **Sustained response (SR) to the treatment with interferon ribavirine in HIV+**

| Source | No | CD4 | SR (IT) | Regime: IF/R |
|---|---|---|---|---|
| Sauleda, et al[265] | 20 | 490 | 8/20 | IF: 3 MU, 3/wk; R: 800-1,200 mg, 6-12 months, according to viral load and genotype |
| Nasti, et al[219] | 17 | >500 | 3/17 | IF: 3 MU, 3/wk; R: 1,000-1,200 mg, 6 months |
| Landau, et al[255] | 51 | 412 | 11/51 | IF: 3 MU, 3/wk; R: 1,000-1,200 mg, 12 months |
| Suciu, et al[252] | 20 | 430 | 8/20 | IF: 3 MU, 3/wk, R: 800-1,000 mg |
| Bochet, et al[194] | 30 | 377 | 6/30 | IF: 3 MU, 3/wk, R: 800-1,200 mg, 6-9-12 months |
| Bini, et al[254] | 32 | 424 | 7/32 | IF: 3 MU, 3/wk, R: 1,000-1,200 mg, 6-12 months according to genotype |
| Perez Olmeda, et al[264*] | 111 | >350 | 17/106** | IF: 3 MU, 3/wk, 24 weeks vs 6 MU, 7/wk, 6 weeks and then 3 MU, 3/wk 18 weeks, R: 800 mg |
| Total | 281 | | 60/276 (22%) | |

SR: sustained reponse; IT: intention-to-treat; IF: alpha-interferon; R: ribavirine; *It is a clinical trial comparing a standard regime of alpha-interferon with an induction regime. ** Poster data (in the abstract: sustained response of 22.3% regarding observed data).

rent study with significantly fewer patients response rates at 24 weeks were similar to the ones found in patients with monoinfected patients (table 9). Because of its high predictive value these results suggest that the sustained virological response in HCV and HIV coinfected patients will be inferior to 20% in these series, resulting in half or less than half the established response for patients with HCV monoinfection.

– The only clinical trial focusing on conventional interferon alpha and ribavirine for 24 or 48 weeks according to genotype in HCV and HIV coinfected patients (32 patients), with HCV monoinfected patients (64 patients) as control group, and with an equivalent sex, race (1/3 of patients were black), genotype (85% genotype 1) and liver cirrhosis (22% of patients) distribution between groups, found a tendency for sustained virological response rate to be inferior in patients with HIV coinfection (22% vs 27% in all patients; 40 vs 50% in genotype 2 or 3; 19 vs 22% in genotype 1).
– The HCV viral load clearance rate with antiHCV treatment was slower among coinfected patients than in monoinfected patients[225,226], possibly in relation to a poorer lymphocytotoxic response against HCV in coinfected patients[227].

Currently, we do not have conclusive results available relating sustained response with the use of higher doses of conventional interferon alpha or the daily administration or the association with induction regimens. Preliminary results point to a higher response rate in patients on combination therapy with con-

TABLE 9. **Combination treatment for chronic C hepatitis in HIV-infected patients. Clinical trials**

| Source | No | Lymphocites CD4+µl | Virologyc response (IT) | Regime: IF/R |
|---|---|---|---|---|
| Sulkowski, et al[228] | 79/82 | 551/533 | WK-12: 20/79 (25,3%) 8/82 (9,8%) | IF: 3 MU, 7/wk, vs 3 MU, 3/wk, 48 weeks; R: 800 mg |
| Cheng, et al[216] | 133 | >300 | WK-24: 15% vs 44% | IF: 6 MU 3/wk, 12 weeks, then 3 MU, 3/wk, 36 weeks; R: growing doses up to 1,000 mg Against Peg-IF alpha 2a (40 kDa) 180 mcg/wk plus R |
| Kostman, et al[255] | 110 | 504 PCRVIH undetectable (57%) | WK-12: 5% vs 23% WK-48: 26% | IF: 3 MU 3/wk, 48 weeks; R: placebo (if at 12 wk PCR+ it is added 800 mg/day) vs 800 mg/day since day 1 |
| Esteban, JI[230] | 27 | 537 PCRVIH undetectable (74%) | WK-24: 48% vs 58% geno 1-4, 28% vs 75% geno 2-3, 89% 75% | IF: 3 MU 3/wk, R: 800 mg/day 48 wk vs PegIF alpha 2b (12 kDa) 1,5 ug/wk; R: 800 mg/day, 48 wk |

SR: sustained response; IT: intention-to-treat; IF: alpha-interferon; R: ribvirine.

ventional interferon alpha given daily vs every other day[228]. These results indirectly indicate a greater probability of response to pegylated interferon-based therapy in coinfected patients.

These results indirectly indicate a greater probability of response to treatment based on pegylated interferon in coinfected patients.

3. *Efficacy of pegylated interferon-based therapies (with and without ribavirne).* Treatment experiences wit pegylated interferon in HCV and HIV coinfected patients is very limited. At least four phase II/III studies with a large number of patients enrolled are currently ongoing with the objective of defining the response rate to therapy, comparing efficacy between conventional interferon alpha plus ribavirine versus pegylated interferon alpha with or without ribavirine, and also to define response according to factors related to HCV infection, HIV infection or demographic characteristics of patients.

Khalili et al have reported the experience with 106 coinfected patients (mean CD4+ count 513 ± 21, 63% with viral load < 50 cop/ml, 80% genotype 1) treated with pegylated interferon alpha 2a (40 kDa) monotherapy for 12 weeks. The virological response rate at week 12 (undetectable viral load or more than 2 log decrease from baseline HCV viral load) was 34%.

In the ACTG A5071 trial, HCV and HIV coinfected patients showed a response rate (undetectable HCV viral load) at week 24 of treatment significantly better in patients treated with pegylated interferon alpha2a plus ribavirine (44%) than patients treated with conventional interferon alpha plus ribavirine (15%)[216].

In a clinical study carried out at the Vall d'Hebron Hospital of Barcelona comparing pegylated interferon alpha 2b plus ribavirine vs interferon 2b plus ribavirine in patients with a good virologic control (74% undetectable plasma HIV) and a good immunological status (mean CD4+ count > 500), the observed response rate (negative HCV PCR) was 58% vs 48%, respectively, a difference found at the expense of patients with genotype 1-4 (47% vs 28%, respectively). The study included few patients (26 and 27 in each arm) but allows speculation over whether adequately selecting candidates may improve efficacy of anti-HCV therapy in coinfected patients[230].

In an observational study of a Spanish cohort involving HCV and HIV coinfected patients with more than 300 CD4+ lymphocytes/µl and controlled HIV infection, 65 cases were treated with pegylated interferon apha 2b plus ribavirine 800 mg/day for 12 months in the case of genotype 1-4 (70%) or 6 months in the case of genotype 3 (30%). Response rate at the end of therapy was 50% (10% in genotype 1-4 and 59% in genotype 3). Sustained response rate was 33%. It is important to remark that in this preliminary analysis a greater proportion of genotype 3 patients were included, due to the shorter duration of therapy in this group[231].

*Factors predicting response to treatment to chronic hepatitis C therapy in HIV coinfected patients.* As in patients with HCV monoinfection, it has been confirmed in at least one study that patients with genotype 2 or 3, low viral load and females[217,231-233] have a greater probability of achieving response to anti-HCV treatment. Other pretreatment factors probably associated with response as grade of fibrosis, time elapsed from HCV infection, weight and race have not been studied yet in coinfected patients.

Several studies have found a relationship between CD4+ lymphocyte count and response to antiHCV treatment[217,233]. Most studies do not include patients with less than 200 CD4+ lymphocytes so that the efficacy of antiHCV therapy in these patients is unpredictable at the present moment.

There are not studies in coinfected patients analyzing the probability of final response to therapy in relation to the interferon or ribavirine doses used (fixed or weight-adjusted), treatment duration (six, twelve months, etc.) or intermediate treatment response. The kinetics of HCV viral load in response to treatment is different in coinfected patients than in the monoinfected ones[225,226]. Therefore, it may be inadequate to translate the predictive factors of response after initiation of anti-HCV treatment obtained from studies with monoinfected patients into the management of the coinfected patient in clinical practice.

*Safety of antiHCV treatment and interactions with antiretroviral therapy in HCV and HIV coinfected patients.* As many studies are series case reports and they have not been published, a lack of reporting exists on anti-HCV treatment tolerance in these patients.

The most numerous series including coinfected patients treated with conventional in-

terferon alpha and ribavirine estimate that 25% to 54% of coinfected patients will interrupt treatment, while this rate is about 20% in the case of HCV monoinfected patients treated for one year[231,233-235].

Safety data, also preliminary, from these studies including patients treated with pegylated interferon and ribavirine show a withdrawal rate of 8.5% at week 12 (5% due to adverse events), 15% at week 24, and 22% at the end of treatment (14% because of adverse events), similar to the rates reported in monoinfected patients (10%-14% due to adverse events)[204,205]. Serious adverse events rate and treatment withdrawal is higher in patients with cirrhosis (21% vs 14% in patients without cirrhosis).

Overall, the spectrum of the adverse events reported in coinfected patients treated with interferon and ribavirine is similar to the observed in monoinfected patients receiving the same treatment. Although no adequate studies exist, it is possible that a potentiation of the adverse events derived form this drugs occur in patients receiving concomitant antiretroviral therapy. To this effect, it is possible that these patients suffer a higher hematologic or central nervous system toxicity due to interferon or a higher incidence of ribavirine-related anemia.

Coinfected patients treated with interferon ± ribavirine may also suffer severe CD4+ lymphocytopenia, lactic acidosis or pancreatitis, adverse events not reported to the date with treatment of HCV monoinfected patients.

CD4+ lymphocytopenia is related with interferon therapy. A significant decrease in the absolute count, although not in the relative number, may occur in coinfected patients treated with interferon alpha[216,217,236]. The CD4+ lymphocyte decrease may reach levels implying a high oportunistic infection risk.

Lactic acidosis, with or without pancreatitis, has been reported in patients treated with ribavirine and antiretroviral therapy[228,237]. Its incidence is low but it carries a high mortality. It is unknown whether these cases represent the expected incidence as a result of antiretroviral therapy irrespective of anti-HCV therapy or if represents the imbalance of mitochondrial function after adding the antiHCV treatment to those patients already receiving antiretroviral therapy. To this effect, it is important to notice that ribavirine is a nucleoside analogue and that a rising risk of symptomatic hyperprolactinemia has been reported in patients on antiretroviral therapy, in relation to the number of nucleoside analogue drugs simultaneously administered[238]. Some authors have reported a significant weight loss in HCV and HIV coinfected patients treated with interferon plus ribavirine and antiHIV therapy simultaneously, as an additional clinical feature of mitochondrial toxicity[239]. We have not found evidences for, nor against, a higher predisposition to the development of lactic acidosis in cirrhotic patients treated with combination therapy including nucleoside analogues, although taking into account the role of liver in lactic acid clearance this association is possible. Also, there are not evidences that routine monitoring of lactacidemia, neither in the context of antiretroviral therapy nor in the context of combined antiretroviral and anti-HCV therapy, might be useful. The interpretation of abnormal levels in patients without symptoms of lactic acidosis may be difficult and costly.

Ribavirine is an inhibitor of the 5′-monophosphate dehydrogenase and it potentiates the metabolism of ddI and abacavir when administered simultaneously[240,241]. It is possible that an increase in didanosine triphosphate, the active metabolite of ddI, is related to the reported cases of pancreatitis in patients receiving both drugs[228,237,242].

Ribavirine decreases zidovudine and stavudine phosphorylation *in vitro*[243-246]. The clinical significance of this interaction is unknown, but no decrease in anti-HIV activity has been reported to the date in patients treated with antiretroviral drugs to which interferon plus ribavirine was added. The role of the anti-HIV activity of interferon alpha[215], especially in its pegylated formulation, compensating the possible decrease in activity of AZT or d4T has not been studied.

No studies exist analyzing the significance of combined therapy with AZT or d4T with ribavirine on ribavirine phosphorylation. A decrease in the ribavirine metabolism is possible under these circumstances, and this could be a factor explaining the inferior efficacy observed to the date with combined the antiHCV therapy in patients with HCV and HIV coinfection compared with HCV monoinfected patients. Two recent studies including more than 150 coinfected patients treated with interferon plus ribavirine, more than 80% were concomitantly receiving anti-

retroviral therapy containing AZT or d4T[231]. In less than 4% of patients a ribavirine dose reduction was necessary, a proportion inferior to the one observed in monoinfected patients treated with interferon and ribavirine. Therefore, the optimal ribavirine dose for the treatment of coinfected patients, taking into account efficacy, interactions with antiretroviral drugs and toxicity, is not sufficiently established.

In summary, more studies are needed in order to better define the efficacy, safety and the more adequate regimens for the treatment of chronic hepatitis C in patients with HIV coinfection. Coinfected patients show a worse treatment response rate than monoinfected patients when treated with interferon plus ribavirine, especially those presenting with genotype 1. Response to treatment is better in patients with genotype 2 or 3, those with lower viremia and those with higher CD4+ lymphocyte counts, although without achieving the response rates observed in monoinfected patients. Furthermore, coinfected patients treated with interferon plus ribavirine have a greater probability of treatment withdrawal, and maybe of presenting adverse events, compared with HCV monoinfected patients.

It is urgent to investigate whether the optimal doses and time of administration of the anti-HCV drugs should be the same in the coinfected patients as in the monoinfected ones, particularly if six-month regimens in genotype 2 or 3 are as effective as one-year regimens, and also if it is possible to predict the final response because of the evolution of HCV viral load after initiation of treatment with the aim of avoiding toxicities and the cost of unnecessary treatment. It is also necessary to establish whether treatment efficacy and tolerance is greater when HCV and HIV infections are treated sequentially or when treated simultaneously. New data are needed on efficacy and tolerance in coinfected patients with less than 200 CD4+ lymphocytes and in patients with stable liver cirrhosis.

*Recommendations on antiHCV treatment in coinfected patients (level C).* AntiHCV therapy in HCV and HIV coinfected patients must be indicated in a individualized way.

The minimum criteria in order to consider antiHCV therapy in these patients are: a persistent GPT elevation, positive HCV viremia, CD4 lymphocyte count superior to 200 cells/µl, stable antiretroviral therapy or no need for such treatment, absence of active oportunistic infections and absence of absolute contraindications for antiHCV therapy (pregnancy, history of serious psychiatric disease, liver cirrhosis Child's grade B or C, heart disease, diabetes mellitus, uncontrolled thyroid disease, active drug or alcohol addiction). Approximately 50% of HIV and HCV coinfected patients will not meet these criteria[247].

It is recommendable to have a liver biopsy before indicating the treatment, especially in patients with genotype 1, who have a low probability of response.

In coinfected patients meeting criteria for antiHCV, the benefits and disadvantages of initiating or defering antiHCV therapy must be considered. To this effect, it will be taken into account:

- The higher response rate in patients with genotype 2 or 3 and in patients with low HCV viral load.
- The smaller probability of serious complications in patients who do not require simultaneous antiretroviral therapy and in patients without liver cirrhosis.
- The risk of presenting toxicity or drug interactions.
- The patient's convenience and availability in order to follow treatment adequately.

Coinfected patients should be informed, before initiating treatment, on the objectives of therapy, the possible adverse events, including teratogenesis when any of the members of the couple is in treatment, and also the close relationship between compliance and treatment efficacy.

In coinfected patients in which anti-HCV therapy is indicated it is recommended to treat with the combination of pegylated interferon (PegIntron 1.5 µg/kg/week or Pegays 180 µg/week) and ribavirine (800-1,200 mg adjusted according to weight and viral genotype) as in monoinfected patients. Treatment duration for patients with genotype 2 or 3 is six months, and 12 months for the rest. Treatment discontinuation should be considered in patients with persistently positive HCV viremia after six months of treatment.

As the kinetics of HCV viremia in response to treatment is different for coinfected patients, it is recommended to use systemati-

cally the intermediate response criteria (at week 4 or 12) defined for monoinfected patients in order to predict the final response. They may be considered in an individualized way to decide the continuation or discontinuation of therapy in patients with difficulties in tolerance.

Coinfected patients receiving anti-HCV treatment must be evaluated before initiating treatment, at least every 2 weeks during the first 4 weeks of treatment, every month during the first six months and every three months until the end of treatment and follow-up, and in any moment the patient reports an unexpected or clinically significant adverse events. As in the case of patients without HIV coinfection, it is recommendable to have a blood test including whole blood count and biochemistry including amylase before treatment initiation, and if abnormal then lipase determination, coagulation tests, quantitative and qualitative HCV viral load levels, HCV genotype, serum CD4+ lymphocyte count, thyroid function and a pregnancy test in women. Besides, it is recommended that all the necessary investigations are performed to rule out other types of liver disease. It is also recommended to take a history, especially relating to adverse events, to perform a physical examination, and have hematology and biochemistry tests every visit. It is recommended to determine HIV viral load and CD4 lymphocyte count after the first month of treatment and then every three months for the rest of treatment. It is also recommended to have a HCV viral load determination by a qualitative technique at the sixth month of therapy in order to decide to continue or discontinue therapy in those patients in which anti-HCV therapy for one year is considered, and after one year of treatment and after six months of treatment discontinuation in those patients who had a negativization of HCV plasma levels. A quantitative HCV plasma level determination will be considered after one months and or after three months of treatment in those in patients in which it has been decided in a individualized way that the result will facilitate the physician´s or patient's decision to continue or discontinue anti HCV therapy at that moment. It is not recommended the routine determination of lactatemia.

Overall, it is recommended to pay attention to symptoms suggesting lactic acidosis and/or pancreatitis, especially in higher risk of potentially develop these complications, those with liver cirrhosis, the patients simultaneously treated with associations including nucleoside analogues with greater mitochondrial toxicity and/or risk of pancreatitis as d4T and ddI. In these cases it can be considered, whenever possible, to change the antiretroviral therapy to a regimen with a lesser potential of toxic interaction during chronic hepatitis C treatment. An adequate information to the patient on the risks and symptoms associated with these adverse events may help to an early consultation and diagnosis.

Finally, it is recommended to monitor closely the antiviral activity of the antiretroviral therapy (HIV viral load determination) in patients concomitantly treated with interferon and ribavirine.

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