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Progress Report

Recommendations for the prevention, diagnosis, and treatment of chronic hepatitis B and C in special population groups (migrants, intravenous drug users and prison inmates)

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ABSTRACT

The global spread of hepatitis B virus (HBV) and hepatitis C virus (HCV), their high chronicity rates and their progression to cirrhosis and hepatocellular carcinoma, are major public health problems. Research and intervention programmes for special population groups are needed in order to assess their infection risk and set up suitable prevention and control strategies.

Aim of this paper is to give health care professionals information on HBV and HCV infections amongst migrants, drug users and prison inmates. The manuscript is an official Position Paper on behalf of the following Scientific Societies: Italian Association for the Study of the Liver (A.I.S.F.), Italian Society of Infectious and Tropical Diseases (S.I.M.I.T.), Italian Federation Department's Operators and Addiction Services (FederSerD), Italian Prison Medicine and Healthcare Society (S.I.M.S.Pe.).

The considered population groups, having a high prevalence HBV and HCV infections, require specific interventions. In this context, the expression "special population" refers to specific vulnerable groups at risk of social exclusion, such as migrants, prison inmates, and intravenous drug users. When dealing with special population groups, social, environmental and clinical factors should be considered when selecting candidates for therapy as indicated by national and international guidelines.

1. Introduction

The global spread of hepatitis B virus (HBV) and hepatitis C virus (HCV), their high chronicity rate and progression to cirrhosis and hepatocellular carcinoma (HCC), make these infections a major public health problem. Research and intervention programmes for special population groups are needed in order to assess their infection risk and set up suitable prevention and control strategies.

Aim of this paper is to give health care professionals information on HBV and HCV infections amongst migrants, drug users and prison inmates, who are usually difficult to reach and to treat.

The manuscript is an official Position Paper on behalf of the following Scientific Societies: Italian Association for the Study of the

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Table 1
Grading System for ranking recommendations in clinical guidelines.

Category, grade	Definition
Strength of recommendation	
A	• Good evidence to support a recommendation
B	• Moderate evidence to support a recommendation
C	• Poor evidence to support a recommendation
Quality of evidence	
1	• Evidence from >1 properly randomized, controlled trial
2	• Evidence from >1 well-designed controlled trial, without randomization; from cohort or case-controlled analytical studies; from multiple time series, or from dramatic results from uncontrolled experiments
3	• Evidence from opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees

Modified from Ref. [1].

Liver (A.I.S.F.), Italian Society of Infectious and Tropical Diseases (S.I.M.I.T.), Italian Federation Department's Operators and Addiction Services (FederSerD), Italian Prison Medicine and Healthcare Society (S.I.M.S.Pe.).

The present recommendations are updated with the results of the most recent Italian and international studies.

The considered population groups, having a high prevalence of HBV and HCV infections, require specific interventions. Therefore, these recommendations are based on the existing guidelines and are integrated with social considerations aimed at reaching high efficacy parameters in the management of these viral infections.

The proposed recommendations are the result of the work of an expert panel on HBV and HCV prevention, diagnosis and treatment in so-called special population groups. In this context, the expression "special population" refers to specific vulnerable groups at risk of social exclusion, such as migrants, prison inmates, and intravenous drug users.

The present work follows the modified classification system based on the recommendations of the Infectious Diseases Society of America-United States Public Health System Grading Service for ranking recommendations in Clinical Guidelines [1] (Table 1).

2. Adherence to treatment

Adherence can be described as a dynamic multidimensional phenomenon related to five classes of factors [2], listed in Table 2. Poor adherence to HBV and HCV antiviral therapies as well as other treatments for chronic diseases is one of the main health problems affecting special population groups. In order to ensure therapy efficacy and demonstrate that improvement in health is a consequence of prescribed treatment, a compliance evaluation is needed.

3. Social assessment

When dealing with special population groups, social, environmental and clinical factors should be considered together with the clinical criteria for selecting a candidate for therapy as indicated by national and international guidelines. Precarious social, economic and labour conditions could lead patients to give priority to their job rather than to their health.

It is important to assess the patient's degree of social "stability", also considering his/her level of social integration (i.e. social disadvantage, precarious working conditions, family support, undocumented migrant status, sedentary or nomadic living conditions, and possibility to relocate or return to the homeland).

Cultural factors can also influence access and adherence to treatment. Patients in fact may not be aware of their chronic disease or could have a different cultural conception of illness and death.

Table 2
Classification of causes of poor adherence to treatment and possible intervention strategies.

Social and economic factors	– User/community support groups adopting a peer-education approach – Directly observed therapy (DOT), where health care operators directly administer the antiviral treatment (dosage control). – Involvement of the family
Health care team and system-related factors	– Patient-based approach and use of a multidisciplinary team for improving adherence (cultural mediators with migrants, psychiatrists and toxicologists with IVDU and prison inmates) – Specialized training for health care workers
Condition-related factors	– Mental health assessment for IVDU and prison inmates – Alcohol abuse evaluation – Assessment of the presence of viral co-infections – Assessment of the presence of other co – morbidities
Therapy-related factors	– Use of SSRI antidepressant drugs in case of IFN-induced depression – Use of growth factors (erythropoietin) in case of anaemia – Patient monitoring
Patient-related factors	– Health education – Counselling before, during and after the treatment – Interventions aimed at increasing patient's motivation

IVDU, intravenous drug use; SSRI, selective serotonin reuptake inhibitor; IFN, interferon.

The major economic, social and cultural problems to be considered when dealing with a patient with viral hepatitis are: poverty, lack of access to health care and medicine, linguistic and cultural barriers, illiteracy, poor health education and lack of familiar and social support. Educating patients, evaluating their social needs and fostering the support of the family can contribute to enhancing access and adherence to therapy. The organization of outreach and peer education activities in user/community support groups can enhance disease management and represent an effective strategy for promoting patient motivation, information and health education [3]. Other actions for improving treatment outcomes in special population groups is directly observed treatment (DOT) administration [4].

4. Special populations

4.1. Migrants

- Systematic HBV and HCV screening for all migrants living in Italy is not recommended [5,6] (A3).

4.1.1. HBV infection

- Screening for people from highly endemic areas for HBV (Asia, Eastern Europe, Africa) is recommended. It should be carried out through serum HBsAg and HBsAb marker detection [6] (A2).
- Due to the significance of perinatal transmission, all pregnant women should be screened, independently from HBV infection prevalence in their country of origin (A2) [5,7]. Furthermore, screening can raise awareness and education amongst the pregnant woman's social environment (family, relatives and friends) (C3).
- HBsAg-positive subjects should be screened for co-infections, such as hepatitis delta virus (HDV) infection [8–16] and human immunodeficiency virus (HIV) infection [16–19], which are highly prevalent due to shared transmission routes [9,20,21] (C3).

- Surveillance for HCC, particularly in Asian and African HBsAg-positive migrants, is also recommended. In fact, these subjects, even in the absence of cirrhosis, are at greater risk for HCC than Caucasians. Indeed, epidemiological data show that these population groups develop the disease complications earlier, due to different routes of infection, viral genotype and the role of cofactors such as aflatoxins.

In spite of the recommendations of American and Canadian guidelines [22–24] to provide earlier surveillance in the above-mentioned non-cirrhotic subjects (ultrasound scan every 6–12 months for Africans over 20 years of age, Asian men over 40 years of age, and Asian women over 50 years of age), no scientific evidence exists proving the real efficacy of this approach. Therefore, personalized screening and assessment of HCC development are needed, prioritizing patients with multifactorial disease (i.e. alcoholism), high levels of viral replication, biochemical and/or histological signs of active disease, and those of Asian and African origin (A2).

4.1.2. HCV infection

- Screening for migrants from areas of high HCV endemicity such as Egypt, the Middle East and Pakistan is recommended [25–27]. As regards other countries, for which no precise data on prevalence exist, screening is recommended only for those people belonging to risk categories such as intravenous and inhalant drug users, prison inmates, and patients with abnormal liver function tests [27,28] (A3).

4.2. Intravenous and inhalant drug users

- In accordance with national guidelines [6,27] and international recommendations [28,29], HBV and HCV screening for intravenous and inhalant drug users and former drug users are recommended, due to the high prevalence of HBV and HCV markers amongst this group (in Italy, 32% for HBV and 60% for HCV) [30] (A2).
- HIV and HDV co-infection testing is recommended, due to the high prevalence in HBsAg-positive drug users of these co-infections and to the risk of fulminant hepatitis [31], together with hepatitis A virus (HAV) screening. Drug users are more likely to contract HAV than the rest of the population and the risk of acute fulminant hepatitis is increased [32] (A2).
- As a group, drug users exhibit a higher rate of psychiatric disorders compared to the general population [33–35].
- In addition to standard pre-treatment hepatological evaluation, drug users should undergo: (1) toxicology testing, (2) psychiatric examination, (3) psychological interview, and (4) social assessment [36] (A1).

4.3. Prison inmates

Prevalence of HBsAg-positive and anti-HCV-positive individuals amongst prison inmates is 6.7% and 38% respectively [40].

- HBV [6,37,38] and HCV [27,39] screening for all prison inmates is recommended due to the numerous risk factors for hepatitis B and C they are exposed to (high concentration of at-risk subjects, overcrowding, sharing of sharpened objects such as razors and nail clippers, risk of transmission through homosexual intercourse, use of unsterilized instruments for tattoos) (A2).
- Prison inmates should be screened for HBV and HCV at their arrival and undergo regular testing during their stay in prison; psychological counselling should also be provided (C3).
- Screening for co-infections is also recommended for this population group (HIV, HAV and HDV if the subject is HBsAg positive) [41] (A2).
- In prison, many patients fall into the difficult-to-treat category: migrants, intravenous drug users, and homeless, alcohol dependent and with psychiatric comorbidity. Therefore, the standard pre-treatment liver evaluation should include psychiatric assessment and careful toxicology history (alcohol and psychoactive substances) [40] (A3).

5. Vaccination strategies

5.1. Hepatitis A virus vaccination

- Pre-vaccination anti-HAV screening is recommended in prisons and drug addiction services [31,42–44] (C3).
- If vaccination is indicated, the HBV/HAV bivalent vaccine (Twinrix®) is recommended, since response rates are higher compared to administration of two different vaccines [45,46] (A2).

5.2. HBV vaccination

- HBsAg and anti-HBs pre-vaccination screening should be performed in order to differentiate infection from immunity [5] (A2).
- Migrants should be vaccinated for hepatitis B if they belong to the following risk categories: origin from highly endemic areas, drug users, non-immunized prison inmates, partners of an infected person, or non-HBV-related chronic liver disease patients. For these groups vaccination should be free of charge and accomplished through a short cycle to allow high compliance and avoid dropouts (if the immunization schedule is very short, it may be less effective and a fourth dose is recommended). Based on expected compliance, the patient can be vaccinated at months 0, 1, 2 and, if possible, again at month 6 [47,48]. For homeless subjects an accelerated hepatitis B immunization schedule (0, 7, 21 days) with a booster at 12 months, results in higher completion rates and similar seroconversion rates compared to traditional schedules [49] (A3).
- The above special population groups should be provided with an easy to carry printed immunization record (C3).

5.3. Anti-pneumococcal and anti-influenza vaccines

- Anti-pneumococcal and anti-influenza vaccines should be offered to subjects with cirrhosis, with opiate dependency not receiving opioid agonist therapy (even if HIV-negative, these patients have a doubled risk of contracting pneumococcal pneumonia and an increased risk of contracting influenza) and to prison inmates [50,51] (A2). Anti-influenza vaccine should not be administered to patients who are receiving interferon treatment, as interferon can induce autoimmune reactions favoured by the immune stimulation caused by vaccine adjuvants (C3).

6. Therapeutic protocols

Candidates to antiviral therapy should be selected on the basis of a cost-efficacy and cost-benefit analysis. Standard inclusion and exclusion criteria indicated in existing national and international guidelines should be considered together with social, environmental and comprehensive clinical factors influencing the above-mentioned special population groups.

6.1. Migrants

6.1.1. Chronic hepatitis B

Indications for therapy follow the cited national and international guidelines [5,52–54]. HBsAg-positive migrants may have different demographic, serological and virological characteristics compared to Italian patients: they are usually younger, often have HBsAg-positive hepatitis and have HBV genotypes other than D, which is the most prevalent in Italy [55–58].

If possible, short-term therapy should be preferred in order to increase compliance, reduce side effects and costs and improve quality of life, especially for difficult-to-treat subjects (C3).

In Reception Centres for Migrants, it is particularly recommended to use the DOT strategy in order to increase adherence (C3).

Therapy should consider the availability of the prescribed medicine in the country of origin of migrants (for instance, tenofovir is not available in China) who may return to their homeland (C3).

6.1.2. Chronic hepatitis C

The most recent national [59] and international [28] guidelines provide therapeutic indications and protocols also suitable for migrants.

Short-term therapy is recommended, especially if subjects are difficult to treat, in order to improve adherence, reduce side effects and costs and improve quality of life (C3).

African patients with baseline neutropoenia (neutrophils <1.500/mm^3) should not be excluded from therapy (B2) [28]. Notwithstanding the higher frequency of constitutional neutropoenia amongst Africans compared to Caucasians, the former do not appear to be at increased risk for serious infections during Pegylated-IFN and ribavirin therapy [28].

In HCV genotype-4 infected patients (prevalent in Egypt, the Middle East and Africa, less common in Europe), ethnic and geographic origin of the infection appears to influence response to treatment.

Several studies carried out in Egypt, the Middle East and Europe show higher rates of sustained virological response (SVR, 65–69% versus 32–40.3%) in Egyptian patients [60–63] compared to European patients [64–67]. Two recent studies [68–69] have also demonstrated that a 24-week course of therapy produced very high SVR rates (86% and 86.7% respectively) when administered to HCV-4 patients with rapid virological response (RVR). Short-term therapy schedules (response-guided therapy) based on RVR and early virological response (EVR) could be therefore proposed to HCV-4 patients, especially to Egyptian patients with low baseline viral load and without other cofactors [69–72].

6.1.2.1. Statements. The duration of treatment can be reduced from 48 to 24 weeks for HCV-4 patients in the following cases (A2) [69–72]:

- RVR (undetectable serum HCV RNA at treatment week 4).
- Baseline HCV-RNA preferably (but not necessarily) <600.000 UI/ml.
- Adequate adherence to Peg-IFN and ribavirin doses.
- Absence of negative cofactors: HBV or HIV co-infection, obesity and metabolic syndrome, advanced fibrosis or cirrhosis.

The duration of treatment can be reduced to 36 weeks for HCV-4 patients in the following cases (A2) [69,71,72]:

- Complete EVR (undetectable serum HCV RNA at treatment week 12).
- Baseline HCV-RNA preferably (but not necessarily) <600.000 UI/ml.
- Adequate adherence to Peg-IFN and ribavirin doses.
- Absence of negative cofactors: HBV or HIV co-infection, obesity and metabolic syndrome, advanced fibrosis or cirrhosis.

6.1.3. Comprehensive clinical and social evaluation

- It is important to assess the level of social "stability" of the patient, which also includes the degree of social integration (i.e. social disadvantage, work precariousness, family support, being an undocumented migrant, sedentary or itinerant condition, probability of relocating or returning to their native country) (C3).
- All conditions interfering with treatment compliance should be considered (homelessness, imminent judicial proceedings, distance from health care services, lack of means of transport, problems with working hours) [73] (C3).
- Treatment can be deferred if the patient is being socially inserted or re-inserted, because side effects of the therapy may compromise the process, especially if the regimen includes interferon (C3).
- If disease progression cannot be monitored or if the patient is likely to return to his/her country of origin (where many drugs are not available), antiviral treatment should be begun immediately (C3).
- Patient motivation is crucial to obtain adherence to therapy: for this reason, multidisciplinary and transcultural counselling should be provided by a team composed of hepatology/infectious disease experts, cultural mediators, psychologists, toxicologists and ethno psychiatrists [3,73–76]. Patient education should also be aimed at advising against alcohol abuse, use of hepatotoxic drugs including NSAIDs (i.e. nimesulide) and herbal remedies during therapy [77–79] (B2).
- Counselling can also provide outreach, peer education activities and the dissemination of multilingual information booklets amongst migrant patients [3,80,81] (B2).
- Providing specific training to health care professionals and involving cultural mediators are useful strategies to overcome linguistic and cultural barriers and to inform the patient on their disease and treatment. This approach strongly increases adherence and success rates [74] (C3).
- A number of co-morbidities can influence SVR rates, such as obesity and metabolic syndrome [82] or alcohol abuse [83], as well as other associated conditions that can reduce adherence or increase side effects such as anaemia [84] and thyroid diseases [85] (B3).
- Amongst the co-morbidities that are more difficult to manage in special population groups, mental disorders represent a major problem requiring in migrants an ethno psychological and ethno psychiatric approach. In fact, in these subjects, mental disorders do not always correspond to the diagnostic categories of Western psychiatry (DSM IV) [86] (C3).

6.2. Intravenous drug users

6.2.1. Statements

- Liver disease evaluation. The criteria listed in the above-mentioned national and international guidelines represent reference documents.
- Comprehensive clinical evaluation.
- Suitability for treatment is a dynamic condition whose criteria should be periodically verified [3]. Each patient should be evaluated with respect to (1) toxicological history; (2) present drug use; (3) possible agonist therapy; (4) psychiatric diagnosis; (5) level of social disadvantage. Urine metabolites analysis (opiates, cocaine, amphetamines and cannabinoids) is also required (A1).

- Adequate counselling and health education carried out in drug addiction services, also adopting a peer education approach (by former drug users), are crucial to obtain motivation [3]. If patient motivation is not sufficient, he/she should not undergo antiviral treatment (B2).
- A multidisciplinary team, including a hepatologist/infectious disease expert, a psychiatrist and a toxicologist, should follow the patient. Patients who underwent treatment in specialized drug addiction services showed higher compliance and enhanced outcome than patients treated in general hospitals and other health services [76,87] (B2).
- Shared therapeutic protocols providing DOT strategy, which includes the supervision of oral therapy administration and the injection of subcutaneous therapy by health care professionals, should be applied [7,88] (B3).
- Pre-treatment psychiatric and psychological screening and psychiatric and psychological monitoring during therapy are recommended [89–90] (A2).
- Administration of questionnaires to evaluate the level of depression is recommended (i.e. BDI – Beck Depression Inventory – self assessment scale, SCID or ASI – Addiction Severity Index) [89] (A2).
- Partial mu-opioid receptor agonist therapy (methadone or buprenorphine) is not a contraindication to antiviral therapy [91,92] (A1).
- Opiate abusers who are not receiving agonist therapy can be treated (especially if they are occasional consumers). Due to the high mortality rate, therapy should be mostly recommended (to motivated patients) in case of advanced liver disease diagnosed through liver biopsy (F3 or F4 fibrosis by METAVIR scoring) or through non-invasive methods (when biopsy is contraindicated) and if the toxicologist considers the patient's condition stabilised [92] (C3).
- For opiate dependent patients with chronic hepatitis C, both buprenorphine and methadone can be used as maintenance agonist therapy [91]. Patients should be receiving a stable maintenance dose when they begin antiviral therapy (B2).
- Axis I and II compensated mental disorders do not constitute a contraindication to therapy if the subject is highly motivated and assisted by a psychiatrist and a multidisciplinary team [73,90] (B2).
- If anti-depressant drugs are needed, serotonin re-uptake inhibitors are preferable (higher tolerability profile), especially escitalopram; antidepressant treatment should begin before antiviral therapy initiation [93,94,95] (B2). If antipsychotics are necessary, second-generation drugs are recommended (olanzapine, aripiprazole) [96–98] (B2).
- In drug users, history of alcohol abuse should be collected through questionnaires (AUDIT, AUDIT-C). In case of alcohol abuse or addiction, treatment and detoxification programmes implemented in collaboration with the treatment team (physicians, educators, psychologists and social workers) are needed [99–100] (B1).
- Moderate and occasional alcohol consumption does not constitute a contraindication to therapy but should be discouraged [28] (C3).
- Acute-phase or decompensated mental disorders, heavy alcohol abuse, or alcohol addiction are temporary contraindications to therapy [73] (B2).

6.3. Prison inmates

6.3.1. Statements

Several aspects should be considered when dealing with detainees:

- During detention health education activities (also using the peer education approach) can be carried out, in particular for persons with no or minimal prior health education (B2) [3,80,81].
- Periodical psychological and psychiatric assessments (and, if needed, anti-depressant or other therapies) should be performed before, during and after IFN treatment, in order to avoid/control the possible appearance of mental side effects [89,94] (B2).
- Antiviral therapy should be initiated only in patients whose detention will be long enough to complete the treatment or in patients who can continue treatment after their release by attending local specialized services (C3).
- When possible DOT strategy, which provides supervision of oral therapy administration and the injection of subcutaneous therapy by health care professionals should be used, similar to anti-HIV treatment in prison inmates [4,88] (A3).
- Opiate agonist therapy (methadone or buprenorphine) [91,92] should be administered to opiate dependent subjects with hepatitis B and C infections in order to reduce transmission, re-infection and the progression of liver disease (B2).
- A multidisciplinary approach through the collaboration of hepatologists, infectious disease experts, clinical psychologists, nurses and prison physicians should be adopted [76] (B2).
- Therapeutic continuity should be promoted by advocating clinical and social cooperation between the services involved in the care of prison inmates, such as prisons, drug addiction services, hospitals and reception centres for migrants. The objective is to limit infections and follow up prison inmates also after their release (C3).
- Alcohol consumption should be evaluated using questionnaires (AUDIT); treatment and detoxification programmes should be carried out in collaboration with the multidisciplinary team (physicians, educators, psychologists and social workers) [99–102] (B2) (B1).
- The participation in controlled and randomized trials in prison will be necessary to optimize dosages and duration of antiviral therapy (A3).

Conflict of interest statement

None declared.

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