MANAGEMENT GUIDELINES FOR

THE HCV/HIV CO-INFECTED ADULT

RECOMMENDATIONS OF A MULTIDISCIPLINARY EXPERT PANEL

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With the evolution of effective antiretroviral therapy, survival in persons with HIV/AIDS has increased dramatically. Simultaneously, there has been a shift in morbidity from that related to opportunistic infections to that related to complications of chronic diseases, such as Hepatitis B, and C, complications of injection drug use and malignancies such as lymphoma. The efficacy of treatment of hepatitis C in the HIV negative patient has improved with the use of combination therapy with interferon and ribavirin. Consequently, treatment of the HCV/HIV coinfected patient is now of increased relevance and importance but complicated due the medical, social and drug related issues of the affected population. Many HCV/HIV coinfected patients also fulfill the criteria for a diagnosis of substance dependence, often with more than one drug of abuse. Assessment and treatment of the addiction is an integral component of the treatment approach and has the potential to improve adherence to and tolerance of anti-viral therapy. Treating addictions first could also minimize the risk of acceleration of liver disease with continued alcohol use, or re-infection with hepatitis C after completion of HCV treatment.

A panel was convened at the request of Health Canada, as part of the Hepatitis C initiative, with the mandate of developing recommendations for the management of the co-infected patient. Funding was obtained from the Hepatitis C Division of Health Canada as part of the Hepatitis C initiative.

Invited to the conference were physicians with expertise in clinical investigation and patient care in the fields of HIV, HCV, and addictions. In addition, physicians with expertise in education, guideline dissemination, clinical virology and family practice were invited to participate. Affected individuals representing the hemophilia, HIV and

HCV communities also contributed to the process. The data from the literature were reviewed and critically evaluated by the relevant experts who made brief presentations to the group. The main issues were discussed in small workshops, and the recommendations developed were presented to and revised by the larger group.

The recommendations of the panel, focus on the diagnosis and treatment of the HIV/HCV coinfected patient. Detailed recommendations for the management of HIV, HCV and addictions are to be found in the relevant journals and guidelines. The recommendations are rated according to the strength and quality of the evidence when and where available, Figure 1 [1]. The written guideline document was reviewed by all the panel members and was sent to 46 other specialists in infectious disease, gastroenterology, virology and hematology and all comments were reviewed and included in the final manuscript.

INTRODUCTION

Epidemiology, Natural History and Treatment of HIV

More than 45,000 Canadians have been reported to be infected with HIV**,** the virus that leads to AIDS [2]. Although men who have sex with men (MSM) remains the predominant risk group for HIV infection overall in this country, an increasing proportion of patients have been infected through intravenous drug use (IDU) and needle sharing with contaminated blood [2]. Injection drug use as a risk factor for HIV is found disproportionately in certain urban cities, and in Vancouver has now become the

predominant risk factor for new cases of HIV. The HIV prevalence rates in Canadian IDU [3] is estimated as 25% in Vancouver,18% in Montreal, 20.5% in Ottawa-Hull, 8% in Toronto, and 14% in Winnipeg [4]. Also, injection drug use as a risk factor for HIV infection is increasing in proportion in certain sub-groups such as women, prisoners and aboriginals. In 1999 46.1% of all new cases of HIV in women in Canada, reported injection drug use as the primary risk factor [2]. A survey of federal prison inmates in 1998 determined that 33% were hepatitis C infected, 2% HIV infected and 24% reported a history of injection drug use [5]. Of the cumulative AIDS cases in Canada, 14.4% were reported in Aboriginals in 1999, compared to <1% in this ethnic group prior to 1990 [2].

Prior to the use of highly active antiviral therapy (HAART), the mean life expectancy of persons with HIV infection was 8-10 years [6]. Since the introduction of HAART, the incidence of opportunistic infections, hospitalizations and HIV associated mortality have decreased dramatically although the mean survival for patients in the HAART era is currently unknown [7-11].

Although no cure is yet realized, combination antiretroviral therapy has been the key to this success. The improvements in outcome were initially attributed to antiretroviral combination therapy with two nucleoside reverse transcriptase inhibitors (NRTI) together with 1-2 protease inhibitors (PI) [12,13]. However, more recent evidence has suggested that equivalent virologic (HIV RNA levels) and immunologic (CD4 cell) responses have been achieved with non-nucleoside reverse transcriptase (NNRTI) in combination with NRTI or triple NRTI based regimens, at least over the short term [14-16]. Treatment is costly, and difficult to adhere to because of the large number of pills,

frequent dosing schedules with specific food and water requirements and frequent short term and long term toxicities (i.e. peripheral neuropathy, diarrhea, renal colic, lipodystrophy etc.) which may be dose limiting [17].

The appropriate time to initiate antiretroviral therapy remains controversial and represents a balance in a given patient between prevention of immune damage and virologic failure resulting from non-adherence or antiviral resistance and quality of life issues related to drug adverse events [18]. No clinical trial data are available to dictate the best time to initiate therapy, although many guidelines based on expert opinion are available [19-22]. The most recent guidelines recommend the initiation of therapy if the CD4 count decreases below 350/mm^3 or if the HIV RNA increases above 5000-30,000 copies/ml [19,20]. The goal of treatment is to suppress viral replication as completely as possible and for as long as possible, enabling stabilization or improvement in immune function and decrease probability of infectious complications. Although optimal responses (viral load suppression to <50 copies/ml) are observed in approximately 60-80% of patients previously naïve to therapy, the proportion responding to and the durability of response to subsequent or salvage combinations is less due to problems with resistance and cross resistance [23,24].

Epidemiology, Natural History and Treatment of Hepatitis C

Hepatitis C, an RNA virus, is transmitted from person to person by contaminated blood. Therefore, persons at risk include those who have been exposed to blood or blood products prior to the introduction of testing for anti HCV, (i.e.: 1990), and those who

have been exposed to contaminated needles used for injection, either of illegal drugs, tattooing, body piercing or whenever reusable needles are used. Sexual transmission of hepatitis C occurs but at a significantly lower rate than either hepatitis B or HIV (e.g. <10%) [25]. Sexual transmission may be increased in the setting of mucosal damage related to trauma or sexually transmitted diseases. Maternal transmission of hepatitis C is <7% unless there is coinfection, where the figure rises to almost 20% [26]. Using antibody screening the prevalence of HCV in Canadians is estimated to be approximately 0,8% [27] Fewer will test HCV RNA positive. In certain populations, e.g. IDU, >80% are infected, typically within the first year of drug use. Long-term follow-up studies suggest that when children and young adults are infected with hepatitis C, persistent infection occurs in approximately 50% [28,29]. In those patients infected at an older age, it is probable that more than 80% become chronically infected [30] Persistent infection is associated with a chronic hepatitis which may range from mild to severe with varying amounts of fibrosis, from none to cirrhosis. Progression of this disease is generally slow, taking place over several decades. However, chronic hepatitis C infection is now the most common indication for orthotopic liver transplantation, as the infection is common and decompensated cirrhosis develops in about 20-30% of patients infected. Cirrhosis is complicated by hepatic decompensation and/or the development of hepatocellular carcinoma. Once cirrhosis is established, the rate of hepatic decompensation ranges from 25% at 10 years (Italy) to 25% at 5 years (United States) [31,32] In the Western world hepatocellular carcinoma is known to complicate cirrhosis secondary to hepatitis C in 1 – 4% per year [31]. Risk factors for rapidly progressive disease include: male gender, age >40yrs at the time of acquisition of HCV, daily alcohol consumption of >50 grams per day (3-4 drinks), obesity and immunosuppression particularly co-infection with HIV [33,34]

The current standard of care for chronic hepatitis C [35] is treatment with a combination of Interferon alpha 2b, 3 million units, 3 times a week, SC and oral ribavirin 1000 – 1200 mg daily given to patients who on an adequate liver biopsy have any inflammation ≥ grade 2/4 and/or fibrosis ? stage 2/4 (METAVIR score [36] i.e.: more than minimal disease. If the Knodell score is being used this would be equivalent to an activity score of **>**6 and a fibrosis score of 0-1. The duration of therapy ranges from 6 months to 1 year depending on the pre-treatment and viral genotype. This therapy is expensive and is associated with many side effects. In those patients who require treatment for six months, cessation of treatment due to adverse events occurs in 12% and in those who require treatment for a year, in 21%. Sustained virologic response rates are less than 50% [37,38]. Long-term follow-up of patients treated for hepatitis C with IFN? **2b plus ribavirin** who have a sustained virological response at 6 months following cessation of therapy have a 97% chance of remaining with undetectable HCV RNA in serum (by qualitative Amplicor) for up to two years – longer follow-up data is not available [39]. Long-term follow-up studies following successful treatment of HCV with IFN monotherapy for up to 6 yrs indicate that lack of detectable HCV RNA in serum is associated with no progression of liver disease as judged by resolution of inflammation and no increase in fibrosis on liver histology [40,41,42]. Sustained virological response is also associated with a decreased risk of hepatocellular carcinoma [43]. Subjectively non-specific symptoms reported in subjects infected with HCV improve with a sustained virological response to therapy [44,45].

Impact of Coinfection with HIV and HCV

As both HIV and HCV share the same transmission routes, co-infection with these two viruses is common [46]. Hepatitis C co-infection is especially prevalent in persons who acquired HIV through the transfusion of contaminated blood or blood products (e.g. hemophilic patients and IDU). The immunodeficiency associated with HIV infection appears to accelerate the course of HCV [47-54]. The impact of treatment of either virus on the natural history of the co-infected patient remains speculative. Chronic liver disease and hepatocellular carcinoma related to HCV are emerging as increasingly common causes of death in persons with HIV, as their overall mortality and life expectancy from HAART therapy increase [55]. Consequently, recent attention has focused on the management of these two viruses in the co-infected patient. It has been recommended that patients with stable HIV be considered for treatment of the Hepatitis C. However, it needs to be recognized that the potential hepatotoxic effects of antiretroviral therapy may be enhanced in the co-infected patient and could have a negative impact on the liver disease due to HCV [56,57]. Further, as the pathogenesis of hepatitis C depends on the host immune response, improvements in immunity following the introduction of HAART could cause a flare-up in hepatitis C related liver disease as has been reported [58,59]. The optimal duration of treatment for HCV in the co-infected patient is unknown.

Special Issues for the Management of the Patient with Co-infection

Management of the patient with HCV/HIV co-infection frequently requires consideration of the treatment of 3 diseases - not only the HIV and HCV but also addiction and

related problems. Without adequate functional control of the addiction issues, it is unlikely that treatment for either the HIV or HCV will be optimal. Not only are there treatment related concerns, such as a decreased ability to adhere to or tolerate the adverse effects of the antiviral therapy, but also there is a risk of progressive liver disease from continued alcohol use or re-infection with hepatitis C following treatment through continued unsafe needle use [60-63]. There is also concern that the subcutaneous use of interferon could serve as a conditioned cue for relapse of needle use and addictive behaviors. There are also special issues related to the importance of education specifically targeted to this group, as well as access to care and treatment. In addition, issues of confidentiality related to the HIV infection may require particular sensitivity when working with certain subgroups, such as prison inmates and Aboriginals.

Identification of the Coinfected Patient (see algorithm)

Because of the overlapping risk categories (IDU, hemophiliac, blood transfusion recipients) co-infection should be considered in all patients diagnosed with either HIV or HCV infection. Counseling guidelines and patient information about the significance of the test results are required. Upon diagnosis of HCV and/or HIV, in addition to referral to the appropriate physician(s) for care, the patient should be made aware of community organizations that can provide support and further information.

Recommendations:

?? All HIV infected patients should have an HCV antibody test (Hepatitis C serology) (**IIIA)**

?? Some HIV infected individuals may have a negative Hepatitis C antibody test despite co-infection although this is now rare with current assays [64]. Those with unexplained abnormal alanine aminotransferase levels (ALT/SGPT) or high risk (e.g. hemophilia, IDU) should have a PCR Amplicor qualitative test for HCV RNA if Hepatitis C serology is negative. **(IIIB)**

?? Hepatitis C infected patients should have HIV testing (ELISA screening and Western Blot if positive) as appropriate for risk: (e.g. all those who have acquired HCV through IDU, hemophilia, contaminated needles, or blood transfusion and those with other risk factors for HIV - i.e. men who have sex with men, unprotected sexual intercourse with an individual from an endemic country, multiple sexual partners, previous STD, known HIV positive partner etc). This needs to be performed before the initiation of therapy for HCV. **(IIIA)**

?? HIV testing must be performed within the context of appropriate pre and post test counseling [65] **(IIIA)**.

?? If the patient is HIV or HCV negative and appropriate risk reduction strategies are not adhered to - repeat testing at intervals is recommended **(IIIA)**.

COMPREHENSIVE MANAGEMENT OF THE COINFECTED PATIENT

I.a Address substance use issues

In order to ensure optimal management of the viral infections, substance use issues must be addressed preferably first or at least concurrently [66]. This is crucial:

- to maximize the potential for adherence to antiviral treatment and follow-up
- to minimize progression of disease (e.g. alcohol has been shown to accelerate HCV progression)
- to prevent Hepatitis C reinfection in HCV treatment responders who clear the virus, as previous infection does not confer immunity
- to enable the patient to appreciate the complexity and the commitment to complicated anti-viral treatment regimens and follow-up
- to better prepare the individual to cope with side effects of treatment (e.g. the flu-like symptoms associated with interferon treatment could simulate opiod withdrawal states)
- to minimize the risk of HCV/HIV treatments worsening or destabilizing a concurrent addiction (e.g. the trigger effect of interferon injections or the unmasking or worsening of coexisting depression - the incidence of which is higher in those with substance dependence)

Recommendations:

?? Comprehensive addictions assessment for anyone with a history of IDU **(IIIA)**

?? Screening for the presence of alcohol disorders (e.g. the C.A.G.E. questions) **(IIIA)**

?? Screening of all patients for the presence of mood disorders **(IIIA)**

?? Referral to a specialist in addictions where appropriate **(IIIA)**

?? Ongoing participation in an addiction treatment program where indicated. The intensity of treatment to be determined by the level of recovery achieved by the individual **(IIIA)**

I.b Address Alcohol Use

Alcohol use (>50 gm/day) has been demonstrated to accelerate the course of liver disease in patients with HCV infection [33,34].

Recommendations:

?? Patients with coinfection should abstain from alcohol intake or minimize to <50 gm/day. Abstinence is preferable. Abstinence is essential for those with a history of prior alcohol abuse. One standard drink contains 13.6 grams of alcohol and is equivalent to one bottle (355 ml) beer (5% alcohol), 150 ml (5 ounces) wine (10-12% alcohol) or 90 ml (3 ounces) fortified wine (16-18% alcohol) or 45 ml (1.5 ounces) liquor (40% alcohol). Fifty grams of alcohol is contained in 3.6 standard drinks).**(II-3 A)**

II.a Assess patient for other hepatic viral infections [35,67]

Recommendations:

?? All co-infected patients should be evaluated for infection and immunity to Hepatitis A (Hepatitis A IgG) and Hepatitis B (HBsAg and HBcAb if the HBsAg is negative). Immunize as appropriate with post vaccination monitoring of antibody response (HBsAb)**,** not required for anti-HAV. (**IIB)**

?? Discuss risk of transmission of one or both infections. All co-infected patients should be made aware that transmission of hepatitis C from person to person is enhanced by co-infection with HIV. (**IIIC)**

III) Develop an HCV Plan (see algorithm)

Prior to considering diagnosis and therapy for HCV, the natural history of the co-infection, the nature of the treatment, the complexity of follow-up, and potential risks and benefits of treatment need to be explained to the patient by informed medical personnel, in a language and at an educational level appropriate to the individual, while respecting cultural differences. It must be ensured that provision is made for access to the necessary expertise, appropriate clinical setting, with available medical care (physical, psychological, and social) and therapy for optimal treatment success.

HCV therapy needs to be coordinated with HIV care (see below) with prioritization of treatment of the dual viral infections.

Currently, the most effective therapy available for the treatment of chronic hepatitis C is interferon alpha-2b combined with ribavirin [37,38]. Treatment with interferon monotherapy is less effective than with interferon combined with ribavirin [36,37]. Ribavirin monotherapy has no effect on serum HCV RNA levels [68]. Recent trials of pegylated interferons indicate that these long acting interferon monotherapies, are almost as effective as the combination of interferon and ribavirin [69,70], although the two treatments have not been directly compared. Pegylated interferons are not currently licensed for treatment in Canada. Trials of pegylated interferon combined with ribavirin are currently ongoing in HIV negative and co-infected patients [71]. The weekly administration of the pegylated interferon could improve adherence in hard to reach populations or those who require directly observed therapy.

Recommendation

?? Patients who are candidates for HCV therapy should receive therapy with a combination of alpha interferon and ribavirin for 24 – 48 weeks depending on genotype, with genotype 1 treated for 48 weeks and genotype 2,3 treated for 24 weeks**. (II-2B)**

Prior to further diagnostic testing, the co-infected patient needs to be evaluated for their potential eligibility for HCV therapy [72]. If the patient is not a candidate for drug therapy, because they have contraindications to the use of either interferon or ribavirin, or if they are unwilling to consider therapy, further invasive diagnostic tests need not be performed.

Absolute contraindications to ribavirin therapy

- renal failure (creatinine clearance <50 ml/min)
- ischemic vascular disease
- pregnancy
- an inability to adhere to abstinence or barrier contraception (either gender)
- hemoglobin <12 g/l

Absolute contraindications to Interferon

- neutrophil count <1.5 x 10^9/L
- platelets <70 x 10^9/L
- current or past psychosis (treated or untreated)
- cardiac arrythmias
- uncontrolled seizures
- autoimmune disease (except controlled thyroid)
- organ transplantation other than liver or bone marrow

Relative contraindications to interferon/ribavirin

- uncontrolled diabetes
- uncontrolled depression
- uncontrolled (daily) alcohol use
- uncontrolled substance use
- psoriasis

In the HIV negative, hepatitis C infected patient, therapy can be considered in those with no absolute contraindications and those in whom relative contraindications can be managed. There is no reason to believe that there should be a different approach in patients co-infected with HIV.

There is no reliable non-invasive test to determine which patients require therapy for their HCV. Although the ALT is the best measure of liver cell destruction, the mean ALT values are similar for those with mild and severe liver disease and the degree of abnormality cannot be used to select patients for therapy [73]. There is no non-invasive measure for the degree of fibrosis. The quantitative HCV RNA level is not a good indication of the extent of liver damage [74-76].

Further evaluation for therapy can be considered in those patients who have persistently elevated serum aminotransferase (ALT) levels over a period of 6 months and who have no absolute contraindications to one or either of these therapies. In HIV negative patients, those with normal ALT are not considered for treatment of HCV [34]. Although patients with mild inflammation and or fibrosis may respond better to treatment than patients with more advanced liver disease, treatment is associated with considerable toxicity and sustained responses remain less than 50%. As these patients have a slow rate of progression, treatment is generally deferred, and the extent of the liver disease is monitored at intervals with liver biopsy [35]. It is unknown whether the risk/benefit ratio is different in co-infected patients with normal ALT and/or minor changes on liver biopsy.

Recommendations:

?? Coinfected patients with normal ALT should have monitoring of ALT every 3 months.**(IIIB)**

?? Coinfected patients with persistently abnormal ALT over a 6 month period can be considered for further evaluation for HCV treatment. **(II-3 C)**

?? Currently antiviral therapy is not recommended for patients with chronic HCV infection who have persistently normal ALT **(II-3 C)**

As liver biochemical test abnormalities are common in persons with HIV, especially those on antiretroviral therapy, an increased ALT value does not necessarily reflect active hepatitis C.

Recommendations:

?? Co-infected patients with abnormal ALT over a 6month period should have a qualitative HCV RNA PCR assay. Only those with a positive assay should be further evaluated for therapy. If a subject tests positive for anti-HCV and negative for HCV RNA and has an elevated ALT – the HCV RNA should be repeated in one year. **(IIIC)**

The final decision regarding the appropriateness of therapeutic intervention is made by the treating physician, in combination with the patient, generally based on the results of examination of a recent liver biopsy [35]. There is, however, controversy as to whether

or not the liver biopsy is essential. Studies have shown that the liver biopsy is the only way to assess the extent of the liver disease, and may occasionally demonstrate disease other than HCV [77], and appears to be safe in patients with coagulation disorders [78-81]. A recent cost effectiveness study and accompanying editorial did not feel the liver biopsy to be required in HIV negative patients [82-83]. The latter study can not be extrapolated to the coinfected patient given the high prevalence of abnormal liver biochemistry in patients with HIV not related to HCV.

As the overall efficacy of this treatment stills remains at less than 50%, and side effects, sometimes serious, are common with this treatment, it is not advocated that all patients chronically infected with hepatitis C undergo therapy. In the HCV positive HIV negative patient, therapy is considered for those who have more than minimal disease i.e.: at least moderate inflammation and/or fibrosis ($\geq$A2F2, Metavir Scoring System). It has been demonstrated that the rate of progression to fibrosis is increased in those with co-infection [47-53]. However, it is unknown whether co-infected patients with lesser degrees of fibrosis and/or inflammation should be considered for treatment.

Recommendation

?? Co-infected patients being considered for HCV therapy should have a baseline abdominal ultrasound, INR and CBC. **(IIIB)**

?? If the ultrasound does not demonstrate obvious cirrhosis, and if there are no contraindications (e.g. factor VIII inhibitors present) and the patient consents, a liver biopsy is recommended to stage the extent of liver disease. **(IIIB).**

?? For patients with normal coagulation, cohort studies have demonstrated a 0.1% risk of hemorrhage and 0.01% risk of death from liver biopsy [84-85]. As this is increased in patients with coagulation disorders of any kind, a transjugular approach which does not perforate the liver capsule, should be considered for liver biopsy **(IIIC)**. For hemophilic patients, consultation with the patients' hematologist to determine replacement therapy is recommended. As a minimum, hemophilic patients should have coagulation factors replaced to 75-100% prior to the procedure, maintained for 48 hours. Where appropriate, patients with increased bleeding risks should be monitored overnight. All patients should be sent home with a clear set of instructions as to what they should do if they develop any untowards symptoms after the procedure.

?? The liver biopsy needs to be adequate in size (3-5 portal tracts) and to be interpreted by an experienced pathologist **(IIIA)**.

?? The Canadian Consensus Guidelines recommends HCV treatment be given to patients who have evidence of progressive liver disease. Patients with more than minimal disease i.e.**:** at least moderate fibrosis and/or inflammation are candidates for therapy (≥A2F2) **(IIIA)**

?? Currently, anti-viral therapy is not recommended for patients with chronic hepatitis C patients who have decompensated cirrhosis. (INR>1.3, elevated conjugated bilirubin, ascites, hepatic encephalopathy and/or variceal hemorrhage) **(II-3 B)**

?? No recommendation can be made for HCV therapy of co-infected patients with lesser degrees of inflammation and/or fibrosis. **(IIID)** A repeat biopsy should be considered in 3-5 years, in those in whom the initial biopsy showed minimal disease i.e.: <A2 and/or <F2 grade of severity. **(III C)**

Responses to therapy for HCV are lower in those with higher HCV RNA levels and those with genotype 1 **[37,38]**.

Recommendations: [35}

?? Prior to initiating therapy for HCV, HCV genotype should be performed **(II-2 A)**

?? Patients who are infected with genotype 1 are recommended to have treatment for 48 weeks **(IA)**

Monitoring HCV Therapy

Once it is established the patient is both suitable for anti-viral therapy for their HCV and requests anti-HCV therapy, treatment can be initiated. The side effects of treatment are maximal during the first two months of therapy. Hence, it is advised that treatment be started at a time in the patient's life (social/work conditions) is stable and not excessively demanding. Patients need to understand that they must make themselves readily available for frequent blood tests and visits to the treating physician/nurse for assessment of side effects during therapy.

Side effects of "combination" therapy and what should be monitored.

Interferon

Interferon causes flu-like symptoms, e.g.: headaches, fever, muscle aches, chills which generally are maximal within the first week of therapy diminishing thereafter [86]. Interferon affects the mood of most patients undergoing therapy and patients and family need to be warned that this therapy is associated with irritability and sometimes overt depression. The patient themselves may not always volunteer the severity of the mood disorder associated with this anti-viral therapy and it may be necessary to interview the partner and/or other household contacts. Other side effects of interferon include: thinning of hair, diarrhea and worsening of psoriasis and/or lichen planus. If the patient is diabetic, the diabetes may become harder to control, and similarly, if there is thyroid dysfunction control of thyroid disease may be lost**.** Thyroid disease denovo and hyperglycemia may develop during interferon therapy. Interferon depresses the bone marrow causing the white blood cell count, particularly the absolute neutrophil count to fall, as well as occasionally inducing thrombocytopenia. Patients with cirrhosis are the most likely to suffer the consequences of bone marrow suppression because of their superimposed hypersplenism. Leukopenia puts the patient at risk of infection, which in those with cirrhosis may occur spontaneously even in the absence of leukopenia. Low platelets may also be a consequence of immune thrombocytopenia related to either the HIV or HCV infection, but hemorrhage secondary to this drug induced thrombocytopenia is unusual.

Recommendations

?? To reduce the flu like symptoms, the patient should take their medication at nighttime and regular strength acetaminophen in appropriate doses may be used to reduce the side effects of Interferon. Non-steroidal antiinflammatory agents should be avoided in patients with significant liver disease e.g. cirrhosis. **(III B)**

?? Patients must be monitored for signs and symptoms of depression. Concurrent anti-depressant therapy is advocated in those patients who become depressed or who are suffering from depression at the time that anti-viral therapy is being considered. Patients who develop severe depression or suicidal ideation should be referred for psychiatric consultation and/or follow-up. **(III B)**

?? Patients with a history of substance dependence will need additional monitoring, support and counseling with regard to the risk of depression and/or addiction relapse. Close collaboration with the patients addictions treatment provider is strongly encouraged. **(IIIB)**

?? Treatment needs to be discontinued if diffuse psoriasis occurs **(III B)**

?? regular monitoring of blood sugar and TSH is essential. **(III B)**

?? Interferon dose reduction is required when the absolute neutrophil count falls below 1.0×10^9/L and interferon needs to be stopped should the absolute neutrophil count falls below 0.5×10^9/L. **(III A).** In patients with cirrhosis, a fall in the absolute

neutrophil count may be associated with an increased risk of sepsis. Hence all patients are required to report any symptoms of infection immediately and receive the appropriate investigations and antibiotic therapy as indicated.

?? Complications secondary to thrombocytopenia are less common and it is not usually necessary to dose reduce unless the platelet count falls to very low levels, e.g.: <40 x 10^9/L. **(III A)**

Ribavirin

The most common side effect of ribavirin is hemolysis, and this occurs in at least 1/3 of those receiving this treatment. [87]. On occasion, the hemoglobin may fall by 2 to 3 g/L in a very short period of time often associated with the onset of sudden fatigue. It is extremely rare that hemolysis would be so severe as to necessitate a blood transfusion. Nevertheless, low grade hemolysis persists throughout therapy, hence the side effects of combination therapy may considerably limit a patient's physical activity. Therapy with ribavirin is also associated with a dry cough, skin rashes, sometimes with pruritus and insomnia.

Recommendations

?? Hemoglobin and reticulocyte count need to be monitored to observe any side effects of ribavirin. Dose reduction of ribavirin is called for when the hemoglobin drops below 10 g/L. **(III C)**

?? Adequate intake of water (>3 litres a day) reduces the symptoms of cough and rash **(III C)**

?? Ribavirin is teratogenic and should not be administered in pregnancy (**IIIB)**

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Overall efficacy of interferon and ribavirin therapy in chronic hepatitis C

Undetectability of HCV in serum (using qualitative testing with a lower limit of detection of 100 copies per ml) at the end of treatment and six months after the cessation of treatment, is the desired response to therapy. A sustained virological response is observed in up to 41% of HIV negative patients with chronic hepatitis C treated with a combination of interferon alpha –2b and ribavirin for up to 48 weeks [37,38]. The sustained virologic rates are considerably higher for those patients infected with genotype 2 or 3, in whom 60 to 64% may have a sustained loss of detectable HCV RNA. In those infected with the genotype 1, sustained virological response rates particularly in those with a baseline viral load >2 million copies per ml or 850,000 IU/ml) are low (10% with 24 wks of therapy and 27% with 48 wks). Efficacy rates for genotype 1 with a lower viral load are somewhat improved (32% 24 wks, 33% 48 wks) [37,38]

Nevertheless the recommendation is to treat all patients infected with genotype 1 for 48 weeks [35]. The number of patients with HIV/HCV co-infection who have received either interferon or interferon plus ribavirin is small, to date the end of treatment responses appear to be similar to those achieved in patients who are HIV negative [88-92]. The data on sustained responses are very limited. Whether or not there truly is a higher relapse rate, as suggested in some cohorts is unclear. A sustained virologic response in HIV negative patients is nearly always accompanied by sustained normalization of aminotransferase levels and improvement in hepatic histology, mainly of the necroinflammatory component [93,94]. Improved hepatic histology may be seen in some patients who do not undergo a sustained virologic response, but whether this histological improvement is sustained long-term following cessation of therapy in the presence of persistent viremia currently remains undetermined [95]. Thus, long-term trials of therapy (4 years) are currently ongoing in patients who have previously not achieved a sustained virologic response, in order to assess its value and safety.

Recommendations

?? Response to therapy should be evaluated by using qualitative testing for HCV RNA by PCR at 6 months, end of treatment and 6 months after the cessation of therapy (lower limit of detection is approximately 50 IU/ml by Amplicor) **(I A)**

?? A liver biopsy at the end of treatment is not indicated **(II-2 E)**

?? If the HCV RNA remains positive at 24 weeks, treatment should be discontinued **(II-2 A)**

Patients who are not eligible for antiviral therapy or those who fail to respond could be considered for liver transplantation if their liver disease becomes decompensated, provided there is stability of the HIV infection. How effective liver transplantation is in this setting needs to be determined.

Recommendation

?? Stable controlled HIV co-infection should not be an absolute contraindication to liver transplantation **(III C)**

IV) HIV PLAN

Treatment of HIV infection should follow recommended guidelines as per HIV infected patients without HCV. Initiation of therapy should be guided by immune status (CD4 cell counts), viral replication (HIV RNA levels) and patients willingness and ability to adhere to combination antiretroviral therapy [19-22]. Combinations based on triple reverse transcriptase inhibitors, non-nucleoside inhibitors and protease inhibitors are all recommended as acceptable therapies [19,20]. For patients with addiction issues, simple combinations with directly observed therapy at street clinics, needle exchanges or methadone treatment centers should be considered.

Should Treatment of HIV infection precede, follow or be concurrent with therapy for HCV?

There is no available peer reviewed literature upon which to make firm recommendations. Until such data can be gathered, all co-infected patients should be encouraged to initiate HCV therapy within the context of a cohort or randomized controlled clinical trial where available.

The theoretical basis for initial management of HCV is based on the concern of the hepatotoxicity of many of the antiretroviral agents in current use, which could be more marked in the presence of HCV [56,57]. However, it remains unclear whether prior therapy for HCV can decrease subsequent toxicity to HIV medications. In addition, the immune restoration associated with HAART therapy could lead to an increase in the immunologic response against HCV and potential worsening of the liver disease [58,59]. In contrast, the beneficial effects of management of HIV have been demonstrated in controlled clinical trials, and should not be deferred to treat HCV first, if HIV treatment is indicated.

Recommendations:

?? In general, HIV should be addressed first and managed according to guidelines **(I A)**. Once the patient has stabilized on combination antiretroviral therapy, consideration could be given to starting therapy for HCV. **(III C)**

?? For patients with stable HIV infection, not requiring immediate therapy (i.e. CD4> 350-500/mm^3, HIV RNA< 5000-30,000 copies/ml) consideration could be given to treatment of HCV first. **(III C)**

?? A treatment holiday from HIV therapy prior to the initiation of HCV therapy in order to decrease drug toxicity cannot be recommended at this time. **(III C)**

?? Because of the complexities and overlapping toxicities associated with therapies for HIV and HCV, the initiation of both treatments at the same time should be avoided. **(III C).** The patient should be stabilized on one treatment before the second is introduced.

What are the preferred antiretroviral agents for the co-infected patient?

All antiretroviral agents have the potential to cause hepatotoxicity. Certain drugs have been associated with an increased risk in the co-infected patient and should be used with caution, especially when there is evidence of baseline liver dysfunction.

Recommendation:

?? Full dose ritonavir and nevirapine should be avoided or used with caution in the co-infected patient **(II-3 B)**.

Should patients with co-infection be monitored more frequently?

Initiation of HAART has been associated with hepatic decompensation and/or increases in serum aminotransferases in HCV coinfection [58,59]. The mechanism of the toxicity and the natural history of abnormalities of liver biochemical tests in the presence or absence of HCV is unknown. The role of immune restoration is speculative. The relationship to lipodystrophy, mitochondrial toxicity, and hepatic steatosis is unknown, but potentially important.

Recommendation:

?? No recommendations are currently available to adjust doses of antiretroviral agents in the setting of liver abnormalities. **(III C)**

?? Co-infected patients should be monitored closely for signs and symptoms of hepatic dysfunction. No recommendation can be made as to what level of ALT should lead to discontinuation of antiretroviral agents. **(III C)**

?? No data are available to make a recommendation as to whether or not the patient can be rechallenged with the same (or class) antiretroviral agent after toxicity resolves.**(III C)**

Should Nucleoside Reverse Transcriptase Inhibitors be Discontinued when Ribavirin is used?

The nucleoside reverse transcriptase inhibitors are taken up into host cells and are then triphosphorylated into active agents by cellular kinases. AZT (zidovudine) and d4T (stavudine) are analogues of thymidine and ddC (dideoxycytidine) and 3TC (lamivudine) are analogues of cytidine. Ribavirin is a guanosine analogue that also requires phosphorylation to an active form by cellular kinases. It has been shown in vitro that ribavirin can competitively inhibit the thymidine kinase required for the phosphorylation of AZT and possibly other agents in this class.[96,97] Ribavirin in vitro can also inhibit the metabolism of DDI resulting in increased concentrations of this agent and theoretical potentiation of the antiviral activity. The clinical relevance of these in vitro observations remains uncertain, but no significant variation in HIV replication was observed in a recent study of "combination therapy" in a co-infected population [98].

Recommendation:

?? There are insufficient clinical data to avoid or select specific agents of the nucleoside reverse transcriptase inhibitors class during concurrent therapy with ribavirin because of concerns of competition for phosphorylation **(III C)**

?? Until more data are available, monitoring for continued control of HIV viral replication one month following initiation of treatment for HCV is warranted. Note that non-specific increases in HIV RNA may be observed at this point. If HIV RNA

increases at one month , the viral load should be repeated 2 months after the initiation of therapy for HCV. If it remains increased, consideration should be given to modification of antiretroviral therapy (or of hepatitis C therapy). **(III C)**

Should certain antiretroviral agents be avoided during concurrent therapy of HCV?

Recommendation:

?? As ribavirin and interferon can cause toxicities that overlap with those of certain antiretroviral agents, their concurrent use should be with caution and careful monitoring **(III C)**.

For example:

Myelosuppression - AZT, hydroxyurea and interferon

Depression - efavirenz and Interferon

Antiretroviral combinations or prophylactic agents may require modification prior to the initiation of treatment of HCV

The Setting for Management of the Co-infected Patient

Initial assessment can take place in the primary care setting. It is important to ensure that all virologic tests, medical imaging and pathology are performed in centers with the

expertise to ensure reliability and reproducibility of test results. Once a co-infected patient is identified, the patients should ideally be referred to a center(s) where patients have access to experts in the management of addictions (where appropriate), HIV and HCV [99,100]. In isolated or rural areas, some of this communication may be via satellite clinics or telephone consultation. Although specialist physician input into the management strategy is felt mandatory, specially trained nurse practitioners or trained primary care physicians (salaried where possible) could be responsible for ongoing care. The physician expert (s) need to be readily available to help with the decision-making and management of complications.

For patients with addiction related issues, to improve acceptance, minimize clinic visits and to improve adherence, the provision of care and education should be moved where possible toward the client population and linked to existing facilities, such as street clinics, methadone clinics or needle exchange sites. In these settings, combined addiction, HIV and HCV management on one site is preferable. Simplifying the HIV regimen, combined with methadone management and directly observed therapy, may be required in certain circumstances. Ongoing education towards risk reduction strategies needs to be structured so as to overcome language and cultural barriers. For first nations individuals, the cultural differences and beliefs in native remedies needs to be recognized and integrated into the treatment plan.

Resource/Funding Issues

The management of co-infected patients is extremely complex. Management teams with the appropriate expertise, and their availability is crucial to optimize outcomes. The process of evaluation (see algorithm) is essential and to ensure that the appropriate patients receive therapy (and vice versa), to minimize drug adverse events, interactions and toxicities, to ensure that the social, psychological and physical needs of patients are met, not only before, but also during and after therapy. Management requires not only the availability and appropriate use of drugs but also the laboratory facilities for monitoring treatment effects and toxicities, personnel to maintain close and regular contact with patients, emergency access to psychiatry and addiction counselors. These programs need to have global or envelope funding so that resources can be allocated as needed and can adapt to changing priorities. In the prison setting, there is a need for increased health care funding and supervision to establish realistic harm reduction strategies, treatment of addictions, and co-infections. Financing of the drugs used in treatment is a provincial matter, but needs to be continually re-evaluated as new data emerge so that patients expected to benefit have access and financial coverage to needed therapies.

Research Priorities

Natural History

1. What is the natural history of HCV in HIV patients treated with HAART? Does HAART change the rate of progression of fibrosis compared with those not on HAART? Does a normal ALT exclude progression of HCV? Is the predictive value of a normal or near normal liver biopsy in the co-infected patient similar to that of the HCV positive but HIV negative patient?

2. What is the incidence of hepatitis C related mortality in persons with HIV?

3. What is the contribution of alcohol use in the progression of liver disease in co-infected patients? What impact does addiction counseling and/or treatment have on this progression?

Treatment Issues

1. Should we treat HIV or HCV first or both simultaneously?

2. What is the natural history and mechanism of liver abnormalities in the co-infected patient on HAART?
3. What impact does addiction counseling and/or treatment have on adherence, tolerance and efficacy of treatment of the viral infections?

4. What are the in vivo correlates of inhibition of phosphorylation of ribavirin and NRTI?

5. What is the best marker to evaluate the response to therapy in the co-infected patients? Is there an early marker of non-response to spare toxicity and cost of longer term therapy?

6. Are there any significant drug interactions between antiviral agents used to treat HIV, HCV and the pharmaceuticals used to treat substance related disorders such as methadone, buphenorphine, antabuse, naltrexone, bupropion and acamprosate?

7. Can substance users with controlled addictions be managed for HCV without the risk of re-infection?

8. Is DOT an effective means of administering therapy for HIV and HCV?

9. Should HIV therapy for the co-infected patient include or spare a protease inhibitor?

10. What is the proper dose of ribavirin for use in the co-infected patient?

11. Is the rate of long term sustained response to HCV in the co-infected patient similar to that of the HIV negative?

12. What is the optimal duration of anti-HCV treatment in the co-infected patient to obtain maximal responses without excessive toxicity? What are the predictors of response to treatment: virologic, immunologic, clinical/behavioural?

13. Is liver transplantation an appropriate treatment for decompensated liver disease from HCV in a patient with stable HIV infection?

14. What are the immunological and virologic changes in either HIV or HCV associated with co-infection? How are these affected by treatment?

15. Can these guidelines improve management of the co-infected patient?

Figure 1

Categories for Quality of Evidence

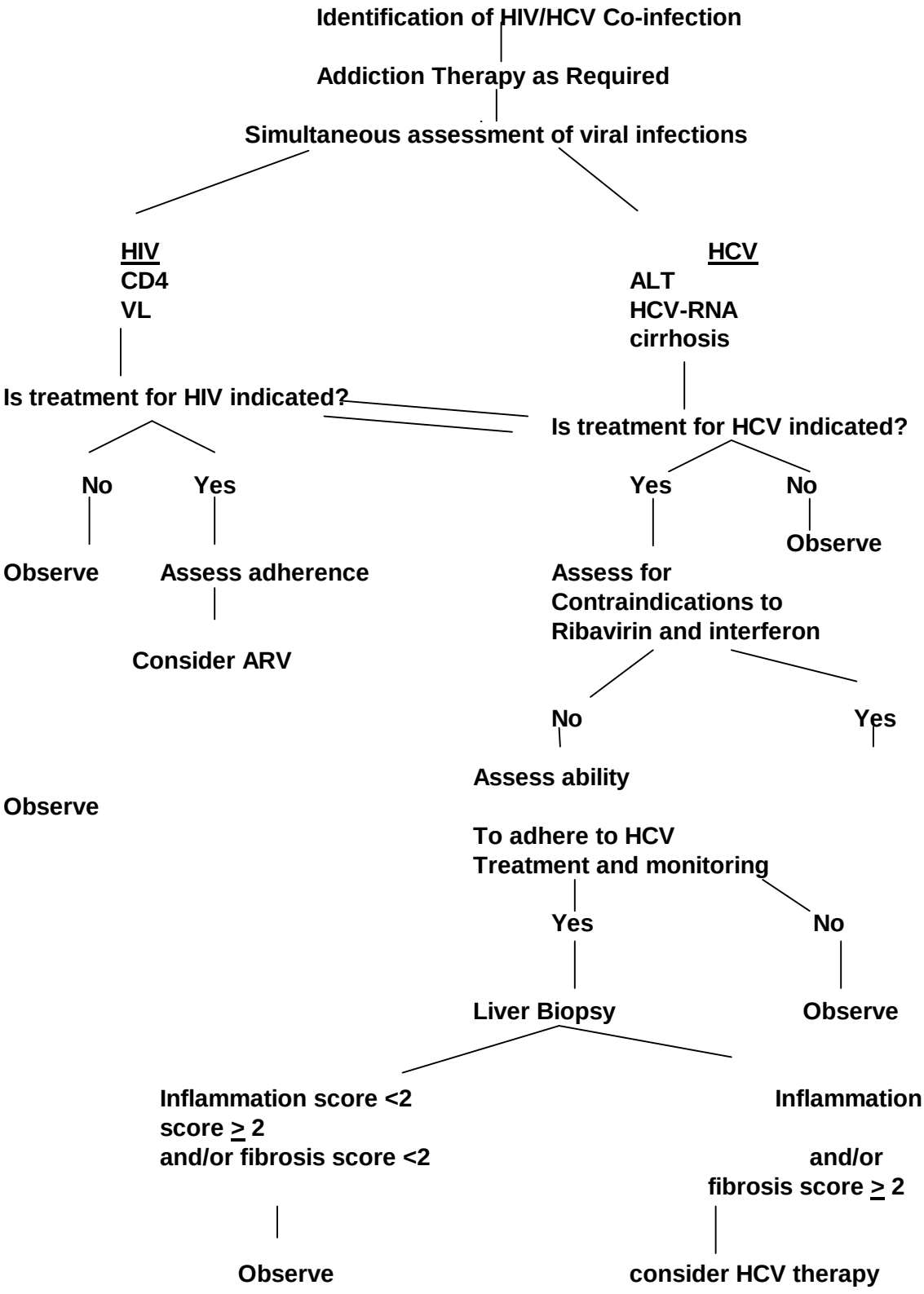
Level of Evidence

Level	Description
I	Evidence from at least one well-designed, randomized controlled trial
II-1	Evidence from well-designed, controlled trials without randomization
II-2	Evidence from well-designed cohort (prospective or retrospective) or case control studies, preferable from more than one investigational center
II-3	Evidence from observational cross-sectional studies or from dramatic results in uncontrolled experiments
III	Opinions of respected clinical experts or evidence from descriptive studies and case reports

Table 2: Categories of strength of recommendations

Category	Description
A	Good evidence to support a recommendation for use of diagnostic test, treatment or intervention
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation for or against use
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use.

ALGORITHM FOR THE MANAGEMENT OF HIV/HCV COINFECTED PATIENTS



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