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adherence to medication for chronic hepatitis C – building on the model of human immunodeficiency virus antiretroviral adherence research

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SUMMARY

Background—Treatment of hepatitis C virus (HCV) infection with pegylated interferon/ribavirin achieves sustained virological response in up to 56% of HCV mono-infected patients and 40% of HCV/human immunodeficiency virus (HIV)-co-infected patients. The relationship of patient adherence to outcome warrants study.

Aim—To review comprehensively research on patient-missed doses to HCV treatment and discuss applicable research from adherence to HIV antiretroviral therapy.

Methods—Publications were identified by PubMed searches using the keywords: adherence, compliance, hepatitis C virus, interferon and ribavirin.

Results—The term ‘non-adherence’ differs in how it is used in the HCV from the HIV literature. In HCV, ‘non-adherence’ refers primarily to dose reductions by the clinician and early treatment discontinuation. In contrast, in HIV, ‘non-adherence’ refers primarily to patient-missed doses. Few data have been published on the rates of missed dose adherence to pegylated interferon/ribavirin and its relationship to virological response.

Conclusions—As HCV treatment becomes more complex with new classes of agents, adherence will be increasingly important to treatment success as resistance mutations may develop with suboptimal dosing of HCV enzyme inhibitors. HIV adherence research can be applied to that on HCV to establish accurate methods to assess adherence, investigate determinants of non-adherence and develop strategies to optimize adherence.

INTRODUCTION

The current recommended first-line treatment for chronic hepatitis C virus (HCV) infection is a combination therapy, which includes pegylated interferon alfa (2a or 2b) administered once-weekly by subcutaneous injection and oral ribavirin taken twice-daily. The goal of treatment is to achieve a sustained virological response (SVR). Sustained virological response indicates long-term viral clearance and results in reduction in liver related morbidity.^{1, 2} Unsuccessful HCV treatment outcomes may be attributed to host factors, viral factors or a combination of the two.^{3–5}

Sustained virological response is achieved in 54–56% of HCV mono-infected patients and in 27–40% of HCV/human immunodeficiency virus (HIV) co-infected patients.^{6–9} HCV treatment is increasingly being tailored to the individual patient based on genotype, co-infection with HIV, severity of liver disease and virological response.^{10–12} The numerous hematological, physical, and neuropsychiatric side effects of HCV treatment can significantly decrease quality of life and often lead to dose reductions and early treatment discontinuation. Proper side effect management can greatly reduce treatment discontinuation.^{13, 14}

MEDICATION ADHERENCE

The term ‘adherence’ is synonymous with ‘compliance’¹⁵ and will hereafter be used as it has a more positive connotation – an active decision by the patient to take a certain action rather than a passive one to obey the provider. Adherence refers to how closely the patient’s actual pill-taking behaviour comes to the recommendations made by the provider with respect to timing, dosage and frequency of medication taking and is usually expressed as a percentage. The general field of medication adherence research has found patient non-adherence (missed doses) in a multitude of medical conditions, such as diabetes, hypertension, arthritis, pulmonary diseases and others.¹⁶ It is estimated that across conditions, patients take on average 79% of the prescribed doses of medication.¹⁷

Preliminary studies on adherence to HIV medication began in the late 1980s and the amount of research in this field began to increase dramatically in 1996 with the introduction of highly active antiretroviral therapy. Drug resistance has been a major limiting factor in successful treatment of HIV infection with antiretroviral (ARV) medications. Optimizing HIV treatment outcomes has been the impetus for the substantial body of research on ARV adherence. Studies on rates and determinants of non-adherence to ARVs led to the development of many effective patient interventions to improve adherence.^{18, 19} Comparable work is just beginning in the field of HCV treatment.

Antiretroviral adherence assessment has been widely integrated into HIV patient care with a multidisciplinary team including the HIV provider, nurse, social worker, psychiatrist/psychologist, clinical pharmacist, all of whom are likely to inquire about medication adherence. Assessment of adherence has not reached the same level of integration in HCV clinical care. There are currently no formal guidelines for assessment of HCV treatment adherence in clinical practice and the extent to which adherence assessment has been incorporated into HCV clinical practice remains unknown. With the goal of improving HCV treatment efficacy, the knowledge gained and lessons learned from HIV ARV adherence research can serve as a roadmap for HCV adherence research and lead to integration into clinical practice.

‘ADHERENCE’ IN THE HCV VS. HIV LITERATURE

The National Institutes of Health Consensus Statement on the Management of Hepatitis C of 2002²⁰ states that ‘patient adherence is critical to the success’ of Hepatitis C treatment, and advises physicians to help patients maximize adherence by adopting an individualized approach in which side effects, depression and substance abuse are managed. Many patients who need HCV treatment, and are eligible, often have numerous risk factors that have been found to be markers of non-adherence in HIV patients, including depression, neurocognitive impairment and current substance use.²¹ Clinician perception that a patient will not be adherent to treatment is a major barrier to patients accessing HCV treatment.^{21, 22} Several studies have shown that when adequate support and resources are provided (e.g. access to food, housing, medical care, medication, psychiatric care, syringe exchange, opioid

substitution therapy), patients with these risk factors can do as well on HCV treatment as those without them.^{23–27}

A comprehensive review of the published literature was conducted to identify studies which assessed patient missed doses of interferon and/or ribavirin in patients being treated for hepatitis C. Primary resources were identified by searches of the U.S. National Library of Medicine's PubMed database using the keywords 'adherence' and 'compliance' separately combined with each of the key words 'hepatitis C virus', 'interferon' and 'ribavirin'. The studies identified were reviewed and selected if missed doses of interferon and/or ribavirin were assessed in patients being treated for hepatitis C. The references in these studies and in review articles were also surveyed for studies which met this criterion. This yielded eight published studies^{27–34} (Tables 1 and 2).

In recent years, the term 'adherence' has increasingly been used in the HCV literature.^{27, 29–38} However, the meaning of 'non-adherence' in HCV often differs from that in the HIV literature.^{21, 39} In HCV treatment literature, 'non-adherence' primarily refers to dose reductions by the clinician due to side effects and to early treatment discontinuation.^{27–29, 33, 35, 37, 38, 40–42} By contrast, in the HIV literature, 'non-adherence' usually refers to the patient missing doses of medication, thereby compromising the prescribed regimen. It would be more accurate to refer to early treatment discontinuation as a failure of medication 'persistence' (the duration of time from initiation to discontinuation of therapy)¹⁵ rather than as non-adherence. The HIV literature is almost exclusively focused on patient medication adherence. In contrast, while HCV literature is actually often focused on patient medication 'persistence', the term 'adherence' is used. Comparisons are also complicated by the fact that dose reductions of pegylated interferon and/or ribavirin are fairly common during HCV treatment, but are not used in HIV treatment due to resistance development. The HCV adherence literature is thus more difficult to interpret, as reported studies may deal with any or all of these concepts (missed doses, persistence and dose reductions) and each can have an impact on HCV treatment outcome.

Drug exposure

To establish clarity in this growing body of literature, we recommend consistent adoption of the term 'drug exposure' in future HCV adherence research. We propose a definition of drug exposure which encompasses all three concepts: the length of time on treatment (persistence), the percent of prescribed doses taken during that time (adherence) and the proportion of the original dose taken (dose reduction) for each medication. For example, three different patients who would all have 75% drug exposure for ribavirin are (1) a patient who took all doses of ribavirin at full dose for 75% of the planned duration of treatment (persistence); (2) a patient who missed doses of ribavirin, therefore taking 75% of the full dose for 100% of the planned duration of treatment (adherence); (3) a patient who took 100% of full dose ribavirin for the first half of their treatment, and then was reduced to half-dose ribavirin therapy, which they took for 100% of the remaining planned treatment course (dose reduction). Although calculating the drug exposure variable is not meaningful for understanding patient behaviour, it is predictive of treatment outcome.

Data on adherence (missed doses) to HCV therapy

While there are well over a hundred published studies of the rates of adherence to ARV medication in HIV disease,⁴³ our comprehensive review yielded only eight published studies which assessed the rates of missed injections of interferon and missed doses of ribavirin independently of dose reductions and early treatment discontinuation.^{27–34} Five of these eight studies^{30–34} report the data on missed doses of interferon and ribavirin independently of dose reductions and early treatment discontinuation (Table 1). These five studies all

investigated once weekly pegylated interferon and twice daily ribavirin treatment and found considerable variability in the rates of patient adherence reported.

The first study, an observational cohort study of 63 HCV/HIV-co-infected patients,³⁰ found that 23% of patients discontinued treatment early; 98% of those patients remaining on treatment self-reported taking all doses of pegylated interferon and ribavirin in the preceding 2 weeks at weeks 12, 24, and 48. The relationship between adherence and virological outcome was not reported.

The second study, the only study to use a multi-method assessment of adherence, incorporated electronic monitoring along with patient self-report.³¹ In this clinical trial sample of 401 HCV mono-infected subjects, at least 95% of subjects self-reported taking all doses of pegylated interferon in the preceding 4 weeks at weeks 4, 12, 24, 36 and 48; those who self-reported taking all doses of ribavirin in the preceding 4 days decreased over time (91% at 4 weeks, 85% at 12 weeks, 83% at 24 weeks, 76% at 36 weeks, 75% at 48 weeks). Much lower rates of adherence were found with electronic monitoring and the rates for both pegylated interferon and ribavirin decreased gradually over the course of treatment. The percent of subjects who took all doses of pegylated interferon in the preceding 4 weeks decreased from 92% at 4 weeks to 74% at 48 weeks; the percent of subjects who took all doses of ribavirin decreased from 74% at 4 weeks to 43% at 48 weeks. Finding lower rates of adherence with electronic monitoring as compared with self-report is consistent with research on ARV adherence in HIV.^{44–46} This study did not report on the relationship of adherence to virological outcome.

The third study, a cross-sectional clinic sample of mostly HCV mono-infected (77%) and HIV-co-infected patients on HCV treatment,³² found that seven percent of patients self-reported missing at least one injection of pegylated interferon in the last 4 weeks and 21% reported missing at least one dose of ribavirin in the preceding 7 days. This cross-sectional study found no relationship between adherence and virological response.

The fourth study also assessed self-reported missed injections of pegylated interferon in the last 4 weeks and missed doses of ribavirin in the preceding 7 days.³³ This was a prospective, real-life, observational study of HCV mono-infected genotype 2 or 3 patients on PEG-IFN/RBV. Patients were categorized as adherent to PEG-IFN if they had taken at least three of four injections in the last 4 weeks and adherent to RBV if they had taken at least 22 of 28 (200 mg) capsules in the last 7 days. At 3 months, 80% of patients were adherent to PEG-IFN and 70–74% were adherent to RBV. At 6 months, these percentages decreased to 69–78% adherent to PEG-IFN and 56–70% adherent to RBV. The relationship between adherence and virological outcome was not reported on.

The fifth study assessed adherence in the first 12 weeks of treatment retrospectively using pharmacy refill data in a sample of 188 largely HCV mono-infected (92%) U.S. Veterans.³⁴ Twenty-six percent of the participants were found to have less than 100% adherence to PEG-IFN and 31% less than 100% adherence to RBV. Using a cut-off of at least 85% adherence to both PEG-IFN and RBV to define good adherence (88% of the sample), this study found a significant relationship between good adherence and achievement of increased HCV suppression and early virological response at week twelve on treatment.

While the remaining three studies^{27–29} assessed patient-missed doses of interferon and ribavirin, the data are not reported in a manner such that distinctions can be made between rates of non-adherence due to patient-missed doses and dose reductions or early treatment discontinuation (Table 2). These were predominantly studies of interferon administered three times weekly and with twice daily ribavirin.

DISTINCTIONS IN ADHERENCE BETWEEN HCV AND HIV THERAPY

There are several unique issues in HCV therapy and adherence research. Hepatitis C virus therapy is time-limited, whereas HIV therapy is usually life-long. Whereas HIV treatment is primarily oral (with the exception of enfuvirtide), HCV treatment involves weekly injection of medication, in many who are former injecting drug users and may choose to come to their provider for weekly injections or arrange to have someone else administer them at home. Therapy with PEG-IFN/RBV often leads to the addition of other medications, as aggressive side effects management can require both additional injectable medications (e.g. epoetin alfa) and/or added pill burden (e.g. antidepressants).

In addition to the higher concomitant rates of depression found in both patient groups (HIV-infected and HCV-infected),^{47, 48} depression is often a serious side effect of PEG-IFN/RBV treatment.⁴⁹ While there is variability across studies in the rates of reported depression, significant symptoms of depression occur in 20–50% of patients on treatment.⁵⁰ This is relevant to adherence in that untreated depression has been found to be one of the most important risk factors for non-adherence in HIV.⁵¹

There is little consensus on the optimal time to initiate HCV therapy, whereas there are guidelines on when to start ARV therapy in HIV-infected patients. In particular, there is less clarity regarding HCV treatment indication with mild hepatic fibrosis staging or when liver biopsy is unavailable. Human immunodeficiency virus treatment has evolved; it is now highly suppressive and commonly requires only once or twice daily dosing, while HCV treatment is still only moderately efficacious and continues to evolve towards not only more effective but also more complex regimens. Side effects from HCV treatment are, in most cases, significantly more severe than those associated with treatment for HIV. While sustained viral clearance or eradication is possible with HCV treatment, ARV treatment only achieves viral suppression to below the current level of detection, but not eradication of HIV.¹ This difference in the treatment goal may impact patient adherence with the potential of achieving HCV eradication motivating higher patient adherence.

UNIQUE ASPECTS OF ADHERENCE TO HCV THERAPY IN HCV/HIV-CO-INFECTED PATIENTS

Adherence in the HCV/HIV patient population has specific issues that warrant dedicated research.³⁹ Given that the majority of HCV/HIV co-infected patients on HCV treatment are also on ARV treatment, there are additional challenges due to the interactions between ribavirin and ARVs, ARV-associated liver toxicity, and risk for development of more severe anaemia.^{52, 53} It is not known whether or not ARV adherence is adversely affected by HCV treatment initiation in HCV/HIV-co-infected patients. In fact, this may be a vulnerable time for ARV adherence and needs further study. Lastly, HIV infection can lead to cognitive impairment and dementia, often in the absence of ARV treatment. Hepatitis C virus has also been found in the cerebro-spinal fluid and its deleterious effects on central nervous system functioning are the subject of ongoing research.^{54–56} Given that diminished cognitive functioning is associated with poorer medication adherence,⁵¹ the presence of dual viruses causing neurocognitive impairment invites specific attention to adherence issues in co-infected patients.

HCV DRUG EXPOSURE PREDICTS HCV OUTCOME

Large randomized trials have shown that adequate drug exposure to PEG-IFN/RBV is a significant predictor of SVR.^{57, 58} Fewer provider-initiated dose reductions have been found to be related to better virological outcome in HCV therapy both for HCV-mono-

infected^{6, 8, 28} and HCV/HIV-co-infected patients.^{9, 29} Ribavirin exposure in particular plays an essential role in achieving SVR and avoiding relapse.^{57–60} The 80/80/80 rule (defined as receiving at least 80% of the planned dose of interferon and 80% of the planned dose of ribavirin for at least 80% of the planned treatment duration) has been considered to be the standard for treatment exposure in HCV therapy²⁸ and was found to be related to SVR in all three studies reported on in Table 2. Recent work documenting that adherence of at least 85% to PEG-IFN/RBV is associated with increased HCV suppression at week 12 and early virological response³⁴ further supports an adherence threshold level in the 80–85% range below which virological suppression of HCV is reduced. This remains lower than the 95% adherence threshold which exists for antiretroviral treatment in HIV patients to prevent development of drug resistance.⁶¹

SPECIFICALLY TARGETED ANTI-VIRAL THERAPY FOR HEPATITIS C (STAT-C): A NEW ADHERENCE CHALLENGE

Hepatitis C virus treatment is evolving with the development of STAT-C agents, oral inhibitors of HCV viral enzymes.^{62–64} These agents directly target HCV viral proteins, similarly to ARVs in HIV treatment. This is in contrast to PEG-IFN, which has potent anti-viral activity but does not act directly on the virus or replication complex.⁶⁵ Multiple mechanisms, each with some experimental support, have been proposed for how ribavirin augments the response rate to PEG-IFN, but it is not yet known which is correct.⁶⁵

Current HCV enzyme inhibitor classes include protease, polymerase and cyclophilin inhibitors, all of which target specific proteins responsible for HCV viral replication. Protease inhibitors target the NS3 and 4a specific proteases; polymerase inhibitors target the ribonucleic acid (RNA) dependent RNA polymerase protein, NS4B; and cyclophilin inhibits the RNA binding of NS5B. These agents have been found to have potent anti-viral activity against HCV, similar to specific ARVs including HIV protease, integrase and entry inhibitors. Several STAT-C agents are progressing through clinical trials, demonstrating enhanced efficacy over current response rates with PEG-IFN/RBV alone. All currently ongoing STAT-C agent trials include PEG-IFN/RBV.

Two types of HCV polymerase inhibitors are under investigation in clinical trials: nucleoside inhibitors (NIs) and non-nucleoside inhibitors (NNIs). Hepatitis C virus NIs resemble HIV nucleoside reverse transcriptase inhibitors (NRTIs), in that they serve as active site inhibitors; NIs act by serving as alternative substrates of NS5B at its active catalytic site.⁶⁶ In contrast, hepatitis C virus NNIs, similar to HIV non-nucleoside reverse transcriptase inhibitors (NNRTIs), do not serve as active site inhibitors but are allosteric inhibitors, resulting in conformational change in the polymerase protein to inhibit binding. These binding site differences between HCV NIs and NNIs may translate into varying propensities for development of resistance.⁶⁶

Several initially promising HCV polymerase inhibitor candidates have been discontinued, due to toxicity problems, such as NM283 due to serious GI toxicity, HCV-796 due to severe hepatotoxicity and R1626 due to ocular toxicity. However, other HCV polymerase inhibitors are moving forward in clinical development. Currently, clinical trial data have been presented for multiple protease inhibitors including telaprevir, boceprevir and ITMN-191(R7227). Both telaprevir and boceprevir are in phase III studies and several others are in earlier clinical trials. In phase II studies of treatment-naïve HCV-mono-infected genotype 1 subjects, the combination of telaprevir with PEG-IFN/RBV resulted in SVR rates from 61% to 68% after 24 weeks of treatment (12 weeks of telaprevir with PEG-IFN/RBV followed by 12 weeks of only PEG-IFN/RBV). Triple combination therapy resulted in

more severe side effects than with only PEG-IFN/RBV, in particular rash, pruritus, anaemia, diarrhoea and nausea.

This increased severity of unpleasant side effects may have a significant impact on adherence to this medication. Completed studies of telaprevir and boceprevir have used every 8 h dosing making optimal medication adherence more difficult, although an ongoing phase II study is investigating twice daily dosing of telaprevir. Randomized studies of antiretroviral treatment in HIV have shown that adherence improves with once-daily dosing.^{67, 68} At least three additional protease inhibitors have reported phase I/II data (TMC435350, BI2011335, MK7009); the first two have single daily dosing regimens. The new generation of HCV agents may allow for shorter treatment duration and will likely be given for only part of the entire treatment course. Upcoming trials combining two or more HCV enzyme inhibitors with PEG-IFN/RBV are under development and may become the standard of care, similar to HIV. These complex regimens will present a new adherence challenge for HCV treatment.

HCV enzyme inhibitor resistance

A major difference between HCV and HIV is that HCV does not integrate into the host cell genome. The rate of mutation and evolution of quasispecies in HCV is, however, comparable to that in HIV⁶⁹ and as HCV treatment continues to evolve and these new classes of small molecular enzyme inhibitors are introduced, resistance due to missed doses may become a serious problem.^{66, 70} For the first time in HCV treatment, failure may not only mean virological *nonresponse*, but failure due to virological resistance, just as in treatment of HIV with ARVs. *In vitro* and *in vivo* resistance to STAT-C agents has already been identified;^{71–75} those to telaprevir were identified in persons with viral rebound in early monotherapy studies, as early as day seven.⁷⁶ Given the high replication rate of HCV and the low genetic barrier to resistance of some of these novel agents (particularly the protease and non-nucleoside polymerase inhibitors), poor adherence may lead to the development of drug resistance. Viral resistance typically occurs when the virus is exposed to drug levels that are below the viral inhibitory level yet above zero, as the virus can then partially replicate and mutant virus strains will emerge under the pressure of the viral enzyme inhibitor.

Just as in HIV therapy, the ability to use multiple STAT-C agents from different classes at once will likely be the future of HCV therapy. This will require careful selection and sequencing of agents, just as in ARV selection. Of particular importance is the development of the mutant A156S/T with telaprevir. This mutation confers cross resistance to boceprevir, the other protease inhibitor, eliminating the possibility of sequential use of these two PIs.⁶⁶ This type of class resistance is found in HIV with the non-nucleoside reverse transcriptase inhibitors and the newly approved class of integrase inhibitors, where specific viral mutations could lead to resistance to other drugs and even entire classes of agents, limiting the use entirely. Fortunately, cross resistance between HCV protease inhibitors and polymerase NIs and NNIs has not been detected, and may enable the use of combination therapy between classes⁶⁶ leading to a more efficacious virological response and decreased resistance emergence. Polymerase NIs may need to be the back bone of combination therapy with either PIs or polymerase NNIs, as they appear to have the highest barrier to resistance.⁷⁷

The relationship between adherence to HIV therapy and virological suppression has been well-documented.^{78–81} High but incomplete levels of ARV adherence (80–90%) were associated with the highest risk of developing drug resistance mutations.⁸² Studies have shown that the rates of non-adherence that most powerfully select for resistant strains vary largely by class of ARV medication.^{83, 84} Parallel studies to determine the adherence-

resistance relationships of STAT-C agents are needed. HCV providers are accustomed to dose reductions as a way of managing patient side effects, but if this strategy is used with STAT-C agents, this will probably increase the risk of resistance.⁷⁰ It is an open question worthy of investigation as to whether the existing adherence threshold of 80–85% in HCV treatment will need to be raised with the introduction of STAT-C agents to prevent resistance and achieve SVR.

APPLICATION OF HIV ADHERENCE ASSESSMENT METHODS TO HCV TREATMENT ADHERENCE/DRUG EXPOSURE

Several methods have been used to assess adherence to HIV medication. The strengths and weaknesses of each method will be discussed as well as the potential to adapt them for the assessment of adherence/drug exposure to PEG-IFN/RBV in HCV treatment.

Clinician assessment

Studies have consistently found that clinician assessment of HIV adherence is poor.^{78, 85, 86} Clinicians tend to overestimate medication adherence and inadequately detect poor adherence. Overestimation can in part be explained by patient awareness that non-adherence will be met with disappointment at best and possibly strong disapproval by their clinician. Regardless of the reason for non-adherence, patients often feel a sense of shame and failure when it comes time to see their clinician and report this non-adherence. Some patients avoid this feared confrontation by failing to attend appointments, attending but not being honest, or distorting their actual adherence behaviour. Communication skills training may help clinicians to assess adherence more accurately and to promote better adherence.⁸⁷ Clinicians treating HCV are strongly encouraged to inquire about adherence in a nonjudgmental manner using open questions at all consultations as it reinforces the importance of it to the patient. The discussion of HCV treatment side effects provides an ideal opportunity for clinicians to address missed doses as this is one of the most frequently cited reasons for missed doses in HIV ARV research.⁸⁸ The effective management of HCV treatment side effects is central to optimizing patient adherence.

Structured self-report

Structured self-report is the most commonly used method of assessing HIV medication adherence due to the low cost and ease of implementation. There are many self-report measures used which vary based on time frame, dimensions (number of pills taken, time of day taken, dietary restrictions followed), wording of questions, use of visual cues and the level of literacy and cognitive ability required to complete the measure.⁸⁹

Self-report measures have been found to overestimate adherence compared to objective measures such as electronic monitoring which uses a microchip placed in the medication bottle cap to record pill-taking events.^{44, 45} For example, studies of HIV antiretroviral adherence have demonstrated mean adherence rates ranging from 80% to 95% when measured by self-report, vs. rates as low as 55–65% when measured by electronic monitoring.^{44–46} Despite these limitations, self-report has been found to be a valid method of assessing ARV medication adherence based on its relationship with virological treatment response in a meta-analysis of 65 studies.⁹⁰

In choosing a self-report measure of ARV adherence, clinicians should take into account the reading level and cognitive status of the patient completing the measure. A Visual Analogue Scale (VAS) has been developed and validated in urban⁹¹ and resource poor settings.⁹² The VAS asks subjects to indicate a point on a line that shows their estimate of how much of each medication they have taken in the past 3 or 4 weeks. The primary advantage of the

VAS is that it is simpler to administer than a structured self-report questionnaire. For settings in which computers are available and patients are computer literate, computer-assisted self-interviewing programmes have been developed and validated to assess HIV medication adherence.⁹³

HIV self-report adherence measures, including the VAS, have been adapted to assess adherence to pegylated interferon injections and ribavirin doses.³² In this adaptation, different time frames were used for assessing adherence to pegylated interferon (last 4 weeks) as opposed to ribavirin (last 7 days) given the different dosing intervals (once weekly vs. twice daily). In designing assessment tools, it is important to consider that if only a single VAS scale is used and the patient reports taking 50% of prescribed ribavirin pills over the last 30 days, it is unclear if this is due to missed doses, patient-initiated dose reduction or treatment discontinuation, physician-instructed dose reduction or treatment discontinuation, or some combination of the above. Self-report measures of drug exposure should therefore assess the following five aspects of drug exposure for interferon, ribavirin and STAT-C agents separately: (1) missed doses (non-adherence), (2) patient-initiated dose reductions, (3) provider-instructed dose reductions, (4) patient-initiated treatment discontinuation (lack of persistence) and (5) provider-instructed treatment discontinuation (lack of persistence).

Pharmacy refill data

Pharmacy refill records have been used to provide an objective, indirect measure of HIV adherence in the analysis of large pharmacy data bases.⁹⁴ This method tends to overestimate adherence (it represents the maximum possible level of adherence given that refill of the prescription does not necessarily mean all medication has been taken and it can exceed 100%) but has been found in several studies to be related to HIV virological outcome.^{79, 95, 96} Pharmacy refill data are most easily employed when patients use one pharmacy for all prescriptions. Pharmacy refill data cannot be used to assess adherence if prescriptions are automatically refilled or monitored by clinicians. If pharmacy refill data are used to assess HCV adherence, it is essential that the data base clearly indicates when HCV treatment has been discontinued early or dose reductions have been made so that these are not mistakenly coded as patient non-adherence.³⁴ In studies in which this is not done, pharmacy refill data can be used to measure drug exposure but not adherence.

Medication Event Monitoring Systems (MEMS)

Medication Event Monitoring Systems technology has been widely used in research studies of HIV medication adherence and is regarded by many as the most accurate method of assessing medication adherence.⁴⁴ The technology uses a microchip placed in the medication bottle cap which records all openings and closings of the bottle. This provides the researcher with precise data on bottle openings for a period of up to 30 days. Potential problems associated with the use of MEMS caps are that patients can open the bottles without taking the medication, patients can take medication for multiple doses out of the bottle at one time, the bottle cannot be used in combination with pill box organizers and they are expensive. This technology can be used to assess adherence to ribavirin and to HCV RNA protease and polymerase inhibitors in clinical trials. In the only study which has assessed adherence to interferon injections by electronic monitoring,³¹ the innovative methodology used was to place the MEMS cap on the sharps disposal container.

Pill count

A review of the assessment of adherence in clinical trials across six chronic illnesses found that pill count was the most commonly used method.⁹⁷ Patients in clinical research studies are often asked to bring their medication to study visits, and the change in the number of

pills (accounting for refills) since the last visit is counted. Patients on HCV therapy could be asked to bring ribavirin pills and STAT-C agents. In some settings, patients can bring in empty interferon syringes or injection pens to assess adherence to injections and deposit in sharps disposal containers whereas in other settings needle stick safety issues may preclude this method of assessment. Potential problems associated with these announced pill counts are that patients may forget to bring their medication to study visits and non-adherent patients may throw out pills prior to the visit ('pill dumps') to avoid being labelled non-adherent. These problems have been cleverly avoided by using unannounced pill counts during home visits in the REACH cohort of marginally housed HIV-positive persons in San Francisco.⁸¹ The unannounced pill count method has also been adapted to be done by telephone.⁹⁸ Either of these methodologies can be applied to HCV adherence research.

Clinical indices

Some researchers have used plasma concentrations of ARV drugs to assess adherence, most often to one particular ARV drug in a clinical trial. This is not a widely used method of assessing adherence, however, given the large number of potential ARV drugs currently used and that drug levels are generally not available for clinical practice and have not been standardized. Monitoring of therapeutic drug levels of either interferon or ribavirin has not been widely employed or validated clinically but has been used in research.⁶⁰

Achieving an undetectable HIV viral load is a widely used surrogate marker for adherence to antiretroviral therapy, especially given its utility as a biomarker for slowing down and reversing progressive immunodeficiency. However, since efficacy of current HCV treatment is low, HCV viral load response to PEG-IFN/RBV is not an acceptable marker for non-adherence. In HIV treatment, macrocytosis has been used as a proxy of adherence to zidovudine. Similarly, some HCV clinicians might view development of side effects of HCV treatment (e.g. anaemia, neutropenia, self-reported neuropsychiatric side effects) as reflective of a high level of adherence. However, given the large variance among patients in the development of side effects and the absence of data on the relationship between HCV treatment adherence and the development of side effects, this is not a useful marker to assess HCV treatment adherence.

Other biological markers have been used in research studies in attempts to identify responders and nonresponders to HCV therapy, including cytokines^{99–101} and peripheral blood lymphocyte subsets.^{102, 103} The host immunological response to HCV therapy is complicated and none of the potential biological markers has been found to be predictive of therapeutic HCV response. We can speculate that if any of these markers becomes validated and results in predictive tests of response to interferon therapy, future studies may assess change over time as additional indices of adherence. Currently, these tests are labour-intensive and their use other than in a research setting would be prohibitive.

Directly Observed Therapy (DOT)

While DOT provides a highly accurate assessment of adherence, the cost and intrusiveness of observing all doses of medication ingestion make it an impractical method of ARV adherence assessment except in very specific settings (e.g. prison, methadone clinic or nursing home). Directly observed therapy is not only a means of assessing adherence but also an intervention to provide additional support to patients at risk for poor adherence.^{24, 104} The pegylation of interferon, allowing for once weekly dosing, has made DOT for interferon more feasible. This would become even more so with biweekly injections of albinterferon alfa-2b which is currently in clinical trials. There is no literature to date on the adequacy of self-injection procedure of pegylated interferon or the at times added injectable haematological growth factors for anaemia or neutropenia. Systematic

research into how patients are adhering to self-injection procedures is greatly needed and DOT would provide the opportunity to study this. At the least, this could be assessed by observing patients self-injecting once early in treatment at a clinic visit and giving feedback on self-injection technique.

CONCLUSIONS

Alongside the existing body of HCV treatment literature on dose reduction and treatment discontinuation and their relationship to virological outcome, comes a growing literature documenting patient non-adherence to PEG-IFN/RBV therapy^{30–34} and its potential relationship with poorer virological response.³⁴ As patients and providers await the approval of novel HCV enzyme inhibitors, which have the potential for complex resistance patterns, the assessment of adherence should be fully integrated into HCV clinical practice and more research on adherence in HCV treatment populations is needed to establish the relationships between levels of adherence and (1) achievement of SVR for distinct HCV genotypes and (2) development of resistance to HCV RNA protease and polymerase inhibitors.

Clinicians should inquire about missed doses of interferon and ribavirin and observe patient self-injection procedure early in treatment. Furthermore, adherence should routinely be assessed by someone other than the clinician using structured self-report at each visit, inquiring about both missed doses and self-reduction of doses. For patients who acknowledge fear of or difficulty with self-injection, administration of weekly injections at the site of care is recommended.

In clinical trials, MEMS and/or pill counts are useful measures to assess adherence to interferon, ribavirin and new STAT-C agents. Clinical trial data should systematically be reported in such a manner that drug exposure as well as its individual components of adherence, persistence and dose reduction for each HCV medication are presented.

The establishment of valid measures for assessing adherence/drug exposure to HCV treatment is necessary to conduct research on the behavioural and neuropsychiatric predictors of success of PEG-IFN/RBV therapy. The identification of these factors will lead to the development of effective behavioural interventions to improve both adherence and persistence and thereby increase treatment efficacy. Subsequently, randomized clinical trials can be conducted to test the efficacy of these behavioural interventions.

With the current lack of data on behavioural interventions to improve adherence of patients on HCV therapy, it is advisable for practising providers to adapt clinic-based strategies, which have been shown to be effective in improving adherence to HIV therapy.¹⁹ These include implementing culturally appropriate patient education, increasing social support, providing medication reminder tools, strengthening the patient-provider relationship, and offering modified DOT if indicated. In addition, HCV providers can benefit from specific training in psychiatric screening and assessment as well as psychopharmacological management of HCV treatment side effects.

From a public health and policy perspective, research on behavioural predictors of achieving SVR will benefit providers and their patients as it will lead to evidenced-based strategies for optimizing HCV treatment outcomes. In addition, providers and patients can utilize this information in their treatment decision-making process and policy makers can be informed of the elements of effective models of HCV treatment provision when allocating public resources.

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Table 1
Five studies which assessed and report on missed doses of interferon and ribavirin

Study	No. of subjects	% HIV-co-infected	Type of study/ HCV treatment	Method of adherence assessment	Interferon adherence	Ribavirin adherence	Adherence - virological outcome relationship
Fumaz <i>et al.</i> 2007 ³⁰	63	100.0	Prospective/ PEG-IFN/RBV	Self-report questionnaire	98–99% report 100% to both at weeks 12, 24, 48		Not reported
Smith <i>et al.</i> 2007 ³¹	401	0	Clinical trial/ PEG-IFN/RBV	Self-report questionnaire + MEMS	Self-report: 98% fully adherent in last 4 weeks at week 4; 97% at week 48 MEMS: 92% fully adherent in last 4 weeks at week 4; 74% at week 48	Self-report: 91% fully adherent in last 4 days at week 4; 75% at week 48 MEMS: 74% fully adherent in last 4 days at week 4; 43% at week 48	Not reported
Weiss <i>et al.</i> 2008 ³²	180	23.2	Cross-sectional/ PEG-IFN/RBV	Self-report questionnaire	93% report taking all 4 of last 4 injections	79% report taking all doses of ribavirin in last 7 days	No association found
Cacoub <i>et al.</i> 2008 ³³	674	0	Prospective/ PEG-IFN/RBV	Self-report questionnaire	80% report taking at least 3 of last 4 injections at 3 months; 69–78% at 6 months	70–74% report taking at least 22 of 28 pills in last 7 days at 3 months; 56–70% at 6 months	Not reported
Lo Re III <i>et al.</i> 2009 ³⁴	188	8.0	Retrospective/ PEG-IFN/RBV	Pharmacy Refill Data	74% report 100% adherence over first 12 weeks of treatment	69% report 100% adherence over first 12 weeks of treatment	Those with greater than 85% adherence had increased HCV suppression and EVR at week 12 compared to those with less than 85% adherence

Table 2

Three studies which assessed but do not separately report missed doses of interferon and ribavirin

Study	No. of subjects	% HIV-co-infected	Type of study /HCV treatment	Method of adherence assessment	80/80/80 Adherence	Adherence - virological outcome relationship
McHutchison <i>et al.</i> 2002 ²⁸	1521	0	3 clinical trials combined – interferon or PEG-IFN + RBV	Pill counts (RBV) and subject diaries	62% took at least 80% of prescribed interferon and at least 80% of the ribavirin for at least 80% of the recommended duration of treatment and were considered 'adherent'	80/80/80 adherence was associated with SVR in genotype 1 but not genotype 2/3 subjects
Sola <i>et al.</i> 2006 ²⁹	157	50.3	Prospective-interferon + RBV	Pill counts (RBV) and self-report questionnaire	76% took at least 80% of prescribed interferon and at least 80% of prescribed ribavirin for at least 80% of the recommended duration of treatment and were considered 'adherent'	80/80/80 adherence was associated with SVR
Sylvestre and Clements 2007 ²⁷	71	1.4	Prospective-interferon + RBV	Return of empty vials (IFN); pill counts (RBV); self-report questionnaire	68% took at least 80% of prescribed interferon and at least 80% of prescribed ribavirin for at least 80% of the recommended duration of treatment and were considered 'adherent'	80/80/80 adherence was associated with SVR