Published in final edited form as:
Int J Tuberc Lung Dis. 2011 November ; 15(11): 1485–i. doi:10.5588/ijtld.11.0068.

Experience with Rifabutin Replacing Rifampin in the Treatment of Tuberculosis

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Abstract

Setting—The use of a rifamycin in anti-tuberculosis treatment regimens is crucial for shortening treatment and achieving favorable cure and relapse rates; rifampin is the recommended rifamycin. Adverse effects (AE) related to rifampin may require its discontinuation.

Objective—Although rifabutin is a rifamycin with activity against *M. tuberculosis* and a different AE profile than rifampin, its use in patients with a rifampin-related AE is not well studied. We reviewed our experience with rifabutin in the treatment of tuberculosis.

Methods—We reviewed tuberculosis cases (2003–2009) who received rifabutin in their treatment regimen. We evaluated the indications for rifabutin use; for patients that experienced a drug-related AE, we categorized the likelihood that the AE was rifampin-related. Using logistic regression analysis, we identified rifampin-related AEs associated with rifabutin intolerance.

Results—One hundred subjects met inclusion criteria. The indications for rifabutin use were a rifampin-related AE in 57 patients (57%), concurrent anti-retroviral therapy (21%), a potential/actual interaction with other medications (14%), and as part of an alternative regimen due to liver disease (8%). Of patients with a prior rifampin-related AE, 80% were successfully treated with rifabutin. Nineteen patients experienced an AE while taking rifabutin. Among patients with a previous rifampin-related AE, only a dermatologic AE was associated with subsequent rifabutin intolerance.

Funding/financial disclosures: The authors have reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in the article.

Author contributions: Dr. Horne had access to and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Dr. Horne: Contributed to study conception and design, data collection, analysis and interpretation of the data, drafting of the manuscript, and critical revision of the paper.
Dr. Spitters: Contributed to study conception and design, interpretation of the data, and critical revision of the paper.
Dr. Narita: Contributed to study conception and design, interpretation of the data, and critical revision of the paper.

Conclusions—Our study suggests that rifabutin is well tolerated by patients who develop rifampin-related AEs. Patients who experienced a rifampin-related dermatologic event may be at increased risk for a rifabutin-related AE.

Keywords

Tuberculosis treatment; rifampin; rifabutin; adverse effects

Introduction

The inclusion of a rifamycin in anti-tuberculosis treatment regimens is crucial for shortening tuberculosis regimen, and achieving high cure and low relapse rates.[1] Rifampin is the preferred first-line member of the rifamycins for the treatment of tuberculosis.[2] Although rifampin is quite well tolerated as part of a tuberculosis regimen, adverse effects may develop including hepatotoxicity, hypersensitivity reactions, dermatologic events, gastrointestinal disturbances, and cytopenias.[1, 3] While some adverse effects will resolve spontaneously or with symptomatic treatment, others may require regimen changes. Rifampin is also a potent inducer of cytochrome p450 enzymes resulting in many drug-drug interactions, some of which merit altering the standard regimen.[4]

Rifabutin is a rifamycin with activity against the *M. tuberculosis* complex. Rifabutin is commonly used in patients with tuberculosis and human immunodeficiency virus (HIV) co-infection who concurrently receive protease inhibitors because rifabutin is a less potent inducer of cytochrome P3A than rifampin.[5, 6] There are multiple well designed randomized clinical trials and many years of experience supporting the efficacy of rifampin in the treatment of TB.[1, 4] Although there are limited head-to-head evaluations of rifampin versus rifabutin in the treatment of tuberculosis, these agents seem to have comparable rates of cure and relapse.[7–10] When using a rifabutin dose of 300 mg per day or less, similar rates of adverse events have been reported for rifabutin and rifampin.[7] However, rifabutin and rifampin differ in their adverse effect profile and rifabutin may have a lower incidence of severe adverse effects.[4, 8] The manufacturer's product information states that the use of rifabutin is contraindicated in patients who have had a clinically significant adverse effect to any rifamycin. The use of rifabutin in patients who are rifampin intolerant has been reported.[3, 11, 12]

We reviewed the use of rifabutin by the Public Health-Seattle & King County Tuberculosis Control Program (TBCP) in the treatment of active TB. In addition to patients who received rifabutin due to a rifampin-related adverse event, we included patients who had other indications for rifabutin to treat active tuberculosis. We were especially interested in the tolerability of rifabutin in patients who had previously had a rifampin-related adverse effect and whether there were patient characteristics that were associated with rifabutin intolerance.

Methods and Materials

The TBCP coordinates treatment for all patients diagnosed with active tuberculosis in King County, Washington, a population of approximately 1.9 million with 130–150 active tuberculosis cases reported per year. We retrospectively reviewed all confirmed tuberculosis cases diagnosed from January 2003 through December 2009 and identified patients who received rifabutin as part of their treatment regimen. All included patients were diagnosed with tuberculosis based on a positive culture for *M. tuberculosis* complex. Cases were excluded if they received rifabutin for less than two weeks and the discontinuation was not due to a rifabutin-related adverse effect. Abstracted data included the clinician's indication

for use of rifabutin, treatment regimens and duration, adverse effects, drug sensitivities, disease characteristics, and demographic information.

Tuberculosis patients were initially treated with standard short-course therapy unless otherwise indicated.[2] When adverse effects occurred in patients on standard short-course therapy, symptomatic management of mild or moderate AEs was attempted and/or dosing frequency was changed to daily administration.[2] In general, the original treatment regimen was not changed for minor symptoms thought to be due to rifampin (e.g. flu-like syndrome). For more severe symptoms and when the responsible medication was not apparent, serial re-introduction anti-tuberculosis medications was performed.[2] TBCP staff physicians (CS, MN) made individualized treatment decisions with respect to use of rifabutin during the period under investigation. Rifabutin was administered at 300 mg daily, twice weekly, or thrice weekly, except in patients receiving concurrent anti-retroviral therapy, in which case dosage adjustments were made based on published guidelines.[13] Patients with baseline hepatic dysfunction or who developed hepatotoxicity while on tuberculosis treatment were placed, at the staff physicians' discretion, on an alternative regimen that included rifabutin, usually in combination with ethambutol and a fluoroquinolone.

Definitions for adverse effects were as follows: liver injury was defined as an alanine aminotransferase (ALT) more than three times the upper limit of normal (ULN) in the presence of gastrointestinal symptoms, an ALT greater than five times the ULN in the absence of gastrointestinal symptoms, or total bilirubin greater than five times the ULN; musculoskeletal event was defined as malaise and arthralgias (without fevers); cytopenia included neutropenia (<1000/ul); gastrointestinal intolerance included nausea, vomiting, diarrhea or abdominal discomfort that was persistent and unresponsive to changes in medication administration (e.g. with meals or at different times) or additional pharmacologic treatment; angioedema included tongue or lip swelling; and dermatologic event was defined as a rash with or without pruritus. Liver injury was graded from 1 to 5 as per the Common Terminology Criteria for Adverse Events.[14]

Adverse effects were considered for attribution to rifampin if they were consistent with known rifampin toxicities and resolved following interruption of anti-tuberculosis agents.[1, 2, 4, 15] They were then categorized as "possible," "probable" or "definite." "Definite" was assigned if the adverse effects recurred on re-challenge with rifampin and resolved with its discontinuation. "Probable" was assigned if the adverse effects did not recur with re-introduction of anti-tuberculous medications other than rifampin. "Possible" was assigned if none of the potentially offending medications were re-introduced. Statistical analyses were performed using Stata 11 (StataCorp, College Station, TX). Bivariate analysis was performed using Fisher exact test for categorical variables and t-test for means. We used multivariable logistic regression analysis to identify rifampin-related adverse effects associated with rifabutin intolerance. Nested models were compared using the likelihood ratio χ^2 test.[16] All tests were two-tailed and the level for determining statistical significance was set at $p \leq 0.05$. The study was approved by the Human Subjects Review Committee of the University of Washington (#39579).

Results

During the seven-year study period, a total of 971 confirmed cases of active tuberculosis were reported to the TBCP. Pharmacy records indicate that 117 (13%) patients received rifabutin for treatment of active TB. Seventeen patients were excluded as medical records could not be located for 15, and two received rifabutin for less than two weeks; 100 patients were included in this study.

Fifty-seven of 100 patients (57%) were placed on rifabutin due to an adverse effect from rifampin. The most common rifampin-related adverse effects were liver injury (53%) and dermatologic event (26%). (Table) Among the 30 patients with rifampin-related liver injury, seven (23%) had grade 2, 21 (70%) had grade 3, and 2 (7%) had grade 4 liver injuries. Among the 55 patients in whom we could categorize the likelihood that an adverse effect was due to rifampin, 16 (29%) were possible, 22 (40%) were probable, and 17 (31%) were definite; we could not categorize 2 patients. The types of adverse effects that were probably or definitely due to rifampin were: liver injury in 14 (36%), dermatologic event in 14 (36%), GI intolerance in 3 (8%), musculoskeletal in 4 (10%), cytopenias in 2 (5%), and angioedema in 2 (5%).

Of the 43 patients placed on rifabutin for indications other than a rifampin-related adverse effect, 21 (49%) were on anti-retroviral therapy, and 14 (33%) had potential or actual interactions with other medications. Eight patients (19%) were placed on rifabutin as part of an alternative regimen due to baseline hepatic dysfunction. The etiologies for liver injury in this group included: hepatitis C infection (5), alcohol abuse with cirrhosis (1), liver transplantation with hepatitis C recurrence (1), and unknown (1). Three did not tolerate rifabutin: two due to liver injury (one with a hepatitis C and one who had received a liver transplant and had recurrent hepatitis C) and one due to cytopenia (who had a history of cirrhosis due to alcohol use).

Of the 100 patients that received rifabutin, 81 (81%) successfully completed therapy with rifabutin. In the 2 years following completion of treatment, we have observed that no patients experienced recurrence of tuberculosis. According to the indication for rifabutin, 81% of patients with a previous rifampin-related adverse effect and 83% of patients with other indications completed therapy with rifabutin. Nineteen patients experienced adverse effects that were potentially rifabutin-related (all the rifabutin-related adverse effects were categorized as probably or definitely due to rifabutin use); eleven of the 19 patients had a previous rifampin-related adverse effect and 8 had another indication for rifabutin. (Figure) Overall, the most common rifabutin-related adverse effects were dermatologic events (8 patients), cytopenia (6), GI intolerance (2), and liver injury (2).

Among the 39 patients with adverse effects categorized as probably or definitely due to rifampin, 28 (72%) did not develop a rifabutin-related adverse effect and were able to complete tuberculosis therapy with rifabutin. Adverse effects related to rifabutin occurred in patients with a prior rifampin-related adverse effect only if that first adverse effect was categorized as probable or definite. The most common rifabutin-related adverse effect was a dermatologic event (6 of 11 patients) and the most common preceding rifampin-related adverse effect was also a dermatologic event in (6 patients). (Figure)

We performed bivariate analysis on a number of patient characteristics to determine whether any of these factors were associated with the development of adverse effects related to rifabutin. (Table) Although most of the factors were not significantly different between patients with or without rifabutin-related adverse effects, there was a difference in development of rifabutin adverse effects by the type of previous rifampin-related adverse effect. In a logistic regression model that evaluated a rifabutin-related adverse effect by rifampin-related adverse effect (liver injury, dermatologic event, GI intolerance, musculoskeletal event, cytopenia), the risk of rifabutin intolerance in patients with a rifampin-associated dermatologic event was 9-fold higher (odds ratio 9.3, 95% confidence interval (CI) 1.6–55) compared to patients with liver injury as a previous rifampin adverse effect; no other rifampin-related adverse effects were associated with our outcome of interest. Collapsing the categories of the least frequent adverse effects (GI intolerance, musculoskeletal event, cytopenia, and angioedema) for inclusion as a single variable in a

logistic regression model (that also included liver injury and dermatologic event) led to a similar result as the full model.

Discussion

Our study expands on the reported experience of using rifabutin in patients that develop rifampin-related adverse effects requiring a change in treatment regimen. Although limited reports have suggested the use of rifabutin in tuberculosis patients intolerant of rifampin due to adverse effects, we are not aware that this is a wide-spread practice among health care professional who treat patients with tuberculosis.[11, 12] We found that rifabutin was well tolerated in our study regardless of the indication for its use. In particular, 80% of patients who had previously developed rifampin-related adverse effects were able to complete tuberculosis treatment with rifabutin. However, patients with a dermatologic event as the rifampin-related adverse effect had a 9-fold higher risk of rifabutin-related adverse effect (CI 1.6–55) compared to patients with liver injury as the rifampin-related adverse effect.

Standard short-course therapy when properly administered in patients with fully susceptible *M. tuberculosis* complex isolates can cure more than 95% of cases of tuberculosis.[9] Rifampin is an essential part of this therapy and has been referred to as the most important anti-tuberculosis agent due to its excellent sterilizing capacity.[2] Tuberculosis treatment regimens that contain a rifamycin for the entire treatment course are superior.17 The use of alternative rifamycins in patients with adverse effects due to rifampin is important for both improving patient outcomes and minimizing resource utilization by tuberculosis treatment programs. Our results suggest an option for retaining a rifamycin in the anti-tuberculosis treatment regimen despite the development of adverse effects due to rifampin.

Rifabutin has similar potency to rifampin in the treatment of tuberculosis.[8–10] Rifabutin has a much longer half-life than rifampin (35 hours compared to 3.5 hours) and there has been concern that this difference in pharmacokinetics was responsible for acquired rifamycin resistance in HIV-positive individuals receiving intermittent treatment for tuberculosis with a rifabutin-containing regimen.[18] However, additional studies suggest that low concentrations of the rifamycin component related to intermittent dosing, rather than the specific agent, determine the risk of acquired rifamycin resistance.[19, 20] A better understanding of the use of rifabutin in different clinical settings is needed now more than ever, as an important barrier to wider spread use of rifabutin, particularly in low and middle-income countries, has been reduced.[17] Rifabutin was recently added to the Essential Medicines List by the World Health Organization and price reductions should increase its accessibility to a global market. While this will allow for a scale-up of anti-retroviral use in patients co-infected with HIV, an additional role is supported by our study. When no rifamycin is used in a tuberculosis treatment regimen, the duration of treatment may be greatly prolonged (e.g., 18 months instead of 6–12 months). While rifabutin will remain more costly than rifampin, the net costs to treatment programs will be determined by a variety of factors including costs associated with personnel and case management.

We presented data on patients with other indications for rifabutin therapy including the co-administration of medications affected by rifampin's induction of cytochrome p450 (e.g. coumadin, methadone). This role for rifabutin has received limited attention.[3] In our study, rifabutin co-administration was well-tolerated and may have limited the need for dosing adjustments to the patient's other medications. We also discussed our experience with rifabutin as part of an alternative regimen due to liver disease in patients with underlying hepatic disease. In this small group of patients, 3 out of 8 patients (38%) developed rifabutin-related adverse effects, 2 of whom showed evidence of liver injury. This result

suggests that caution should be exercised in the use of rifabutin as part of a “liver-sparing” regimen in patients with underlying liver disease.

The literature reports similar rates of hepatic injury with rifampin and rifabutin in the treatment of tuberculosis.[7] In our study, 11 of 14 subjects (79%) who had liver injury that was probably or definitely rifampin-related successfully completed therapy with a rifabutin-containing regimen. However, studies have demonstrated that a very high percentage of patients who develop evidence of liver injury while on treatment for tuberculosis may be successfully re-challenged with all the original medications without the recurrence of liver injury.[21, 22] It is possible that many of our subjects with probable rifampin-related liver injury could have been successfully retreated with rifampin. However, it is important to note that the two patients with definite rifampin-related liver injury (both grade 3) were successfully treated with rifabutin-containing regimens.

There are several limitations to our study. The small sample size limited our ability to adjust for potential confounders and detect significant associations between patient characteristics and rifabutin-related adverse effects, particularly for the less common rifampin-related adverse effects. Clinical decision-making was not standardized, reducing the confidence with which inferences can be drawn from the findings. Finally, we did not have any patients that experienced life-threatening adverse effects related to rifampin (e.g. anyphylactic events); we would caution against the use of rifabutin under such circumstances.

We would advocate for greater research into the use of rifabutin in the treatment of tuberculosis in different clinical settings. Our study supports cautious use for a routine role for rifabutin in patients with non-dermatologic intolerance to rifampin.

Acknowledgments

This work was supported by the National Institute of Allergy and Infectious Diseases at the National Institutes of Health [K23 AI 85036-01 to DJH; and the Firland Foundation].

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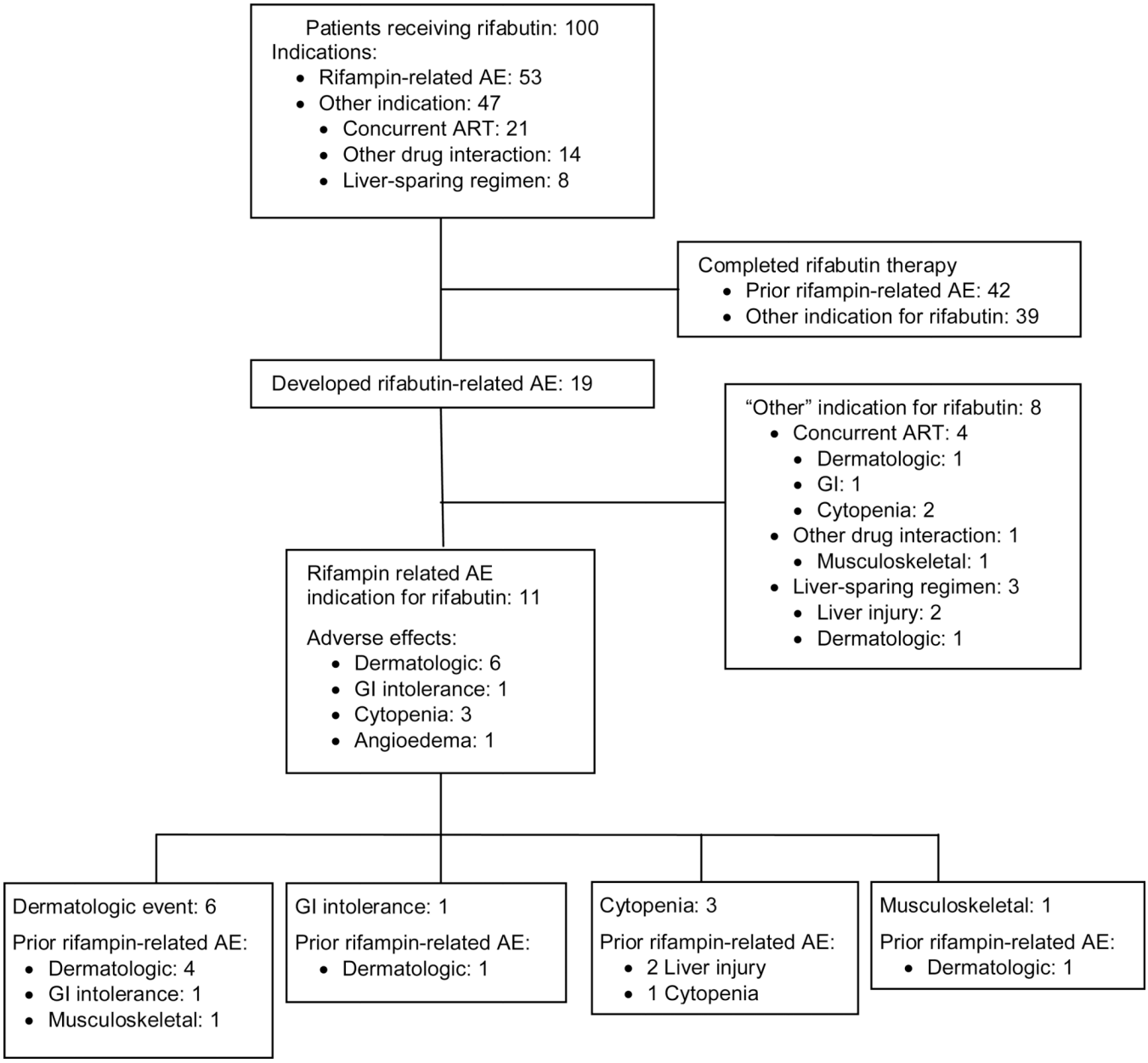

Figure.

Diagram of study patients and outcome according to development of rifabutin adverse effect (AE). "Other indication" is defined as an indication for rifabutin other than a rifampin-related AE including concurrent anti-retroviral therapy (ART) use, potential or actual interaction with other patient medications, or as part of a liver-sparing regimen due to underlying liver disease.

Table

Characteristics of Patients Who Received Rifabutin for Treatment of Tuberculosis[a]

Variable	Rifabutin for other than rifampin AE (N = 43)	Treated with rifabutin due to rifampin related AE (n=57)		P Value[b]
		No rifabutin AE (N = 46)	Rifabutin AE (N = 11)	
Age in years, mean (±SD)	47 (±14)	46 (±18)	52 (±19)	0.34
Male (%)	31 (72)	27 (59)	5 (45)	0.51
Foreign born	22 (51)	33 (72)	6 (55)	0.30
Race/Ethnicity				0.58
Asian	6 (14)	22 (48)	6 (55)	
Black	15 (35)	8 (18)	3 (27)	
Hispanic	6 (14)	7 (15)	0	
Native American	2 (5)	7 (15)	1 (9)	
White	14 (32)	2 (4)	1 (9)	
HIV-infected (n, %)	23 (53)	3 (7)	2 (18)	0.24
Risk factors for liver injury[c]	14 (33)	15 (33)	1 (10)	0.15
TB site				
Pulmonary	28 (65)	29 (63)	8 (73)	0.89
Extrapulmonary	7 (16)	9 (20)	2 (18)	
Both	8 (19)	8 (17)	1(9)	
Time on rifampin (weeks), mean (±SD)	4 (+7)	6 (+6)	9 (+13)	0.32
Time on rifabutin (weeks), mean (±SD)	25 (±12)	30 (±12)	13 (±13)	<0.001
Total treatment time (weeks), mean (±SD)	35 (±10)	39 (±12)	36 (±19)	0.59
Indication for rifabutin				0.046
Liver Injury		28 (61)	2 (18)	
Dermatologic event		9 (20)	6 (55)	
GI Intolerance		3 (6)	1 (9)	
Musculoskeletal event		3 (7)	1 (9)	
Cytopenia		1 (2)	1 (9)	
Angioedema		2 (4)	0	
Liver-sparing	8 (19)			
ART Interaction	21 (49)			
Other drug interaction	14 (33)			

Abbreviations: AE – adverse effect; SD – standard deviation; HIV – human immunodeficiency virus; ART – antiretroviral therapy

[a] Values are expressed as number (percentage) unless otherwise indicated.

[b] P values for comparison of columns “No rifabutin adverse effects” and “Rifabutin adverse effects” using Fisher exact test for categorical variables and t test for means.

[c] Risk factors for hepatic injury included: alcohol abuse, chronic hepatitis B, cirrhosis, hepatitis C