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Adherence to nucleos(t)ide analogues for chronic hepatitis B in clinical practice and correlation with virological breakthroughs

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SUMMARY. Medication adherence is important for the success of nucleos(t)ide analogue (NUC) treatment for chronic hepatitis B. The aims of this study were to determine adherence to NUCs and factors associated with NUC adherence and to correlate NUC adherence with the occurrence of virological breakthroughs in patients with chronic hepatitis B. Consecutive patients with chronic hepatitis B receiving NUC were asked to complete a survey every 3 months. Adherence was also assessed by healthcare providers in the clinic. Adherence rate was defined as the per cent of days the patients took their hepatitis B virus medications during the last 30 days. A total of 111 patients were studied. The mean age was 47.7 years, 73.9% were men, 57.7% were Asian, 42.3% had postgraduate education and 80% had private insurance. Sixty-nine (74.1%) patients reported 100% adherence in the survey, while 78 (83.9%) reported 100% adherence to their healthcare providers. Patients with 100% adherence based on the survey were older ($P = 0.02$), more likely to be men ($P = 0.006$), and had higher annual household income ($P = 0.04$) than those with <100% adherence. In the 80 patients who completed three surveys, viral breakthrough was observed in 1/46 (2.2%) with 100% adherence on all three surveys, 1/18 (5.6%) with <100% adherence on one survey and 3/16 (18.8%) with <100% adherence on ≥2 surveys, ($P = 0.06$). In conclusion, adherence to NUC therapy in our patients with chronic hepatitis B was high but self-reporting of adherence to healthcare providers may be inflated. Patients with chronic hepatitis B with better adherence to NUC therapy had a trend towards a lower rate of viral breakthroughs.

Keywords: antiviral resistance, antiviral therapy, HBV DNA, hepatitis B treatment.

INTRODUCTION

There are seven approved therapies including five nucleos(t)ide analogues (NUCs) and two interferon alpha formulations for the treatment of chronic hepatitis B (CHB). NUCs have potent antiviral activity, are administered orally and have very few side effects but they do not eradicate hepatitis B virus (HBV). Therefore, most of the patients require long durations of treatment to maintain viral suppression and to achieve clinical benefit. Long duration of treatment is associated with increasing risk of drug resistance. Analysis of phase III clinical trials of NUCs found that virological breakthrough (VBT) occurred in 1.6–13.8% of patients after 1 year of treatment; however, genotypic resistance (GR) was not confirmed in any of the patients who experienced VBT while receiving NUCs that have high genetic barrier to resistance, such as entecavir and tenofovir [1–7]. These results suggest that a major cause of VBT may be poor adherence to medications.

Medication adherence has been shown to correlate with clinical response and treatment outcome in many medical conditions [8–12]. Studies in patients receiving nonboosted protease inhibitor-based regimens for human immunodeficiency virus (HIV) infection found that near-perfect adherence (≥95%) was required to maintain viral suppression and to prevent drug resistance, whereas moderate to high levels of adherence (70–95%) to non-nucleoside reverse transcriptase inhibitor-based regimens was sufficient for optimal virological response [12–15]. Similarly, hypertensive patients with at least 80% adherence to antihypertensive agents were less likely to develop coronary artery disease, cerebrovascular disease and congestive heart failure, and hypercholesterolaemic patients with at least 90% adherence to statins had fewer nonfatal coronary artery events [9,10].

Abbreviations: CHB, chronic hepatitis B; GR, genotypic resistance; HBV, hepatitis B virus; HIV, Human immunodeficiency virus; NUCs, nucleos(t)ide analogues; VBT, virologic breakthrough.

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Data on medication adherence in patients receiving NUCs for CHB are limited. Our previous study using a national pharmacy claims database of 11 100 subjects found that the mean adherence rate during a 1-year period was 87.8 ± 19.1% [16]. Because the database was not linked to any clinical information, the relationship between adherence and virological response or breakthrough could not be determined.

The aims of the current study were (i) to determine medication adherence using a standardized questionnaire among patients receiving NUCs for CHB, (ii) to determine the factors associated with medication adherence, (iii) to correlate medication adherence with VBT and confirmed GR and (iv) to correlate self-reported adherence with provider assessment of medication adherence.

MATERIALS AND METHODS

Study patients

Adult patients with chronic hepatitis B receiving NUCs attending the liver clinic at the University of Michigan Health System were eligible to participate in this study. Exclusion criteria included patients with hepatitis C, hepatitis D or HIV co-infection; patients with decompensated liver disease or prior liver transplantation; patients with impaired renal function requiring dose adjustment of NUC; immunosuppressed patients receiving HBV antiviral prophylaxis; pregnant patients; and patients who were not fluent in English or were unable to provide consent.

Study design

This study was conducted between May 2009 and October 2010. The protocol was approved by our institutional review board. Eligible patients were enrolled during a scheduled clinic visit. At enrolment, patients were asked to complete a confidential questionnaire and return to the research fellows (WC and CH) who were not involved in the care of the patients. The healthcare providers (6 hepatology faculty and 2 physician assistants) also assessed the participants' medication adherence during the clinic visit and documented the information in the clinic notes. Patients were asked to complete a shorter version of the questionnaire every 3 months for up to 1 year. Medical records of each patient were reviewed to retrieve information regarding medical history, current and previous HBV treatments and virological response and breakthroughs.

Self-reported questionnaire

The initial questionnaire collected data on demographic, education, household income; HBV treatments, health insurance and copayment for HBV medication (see supplementary Table S1). In addition, patients were asked four questions relating to medication adherence, the key question being how many days they missed their HBV medication in the last 30 days. The follow-up questionnaire (see supplementary Table S2) collected data on current HBV treatment and three questions relating to medication adherence.

Definitions

Adherence was defined as the per cent of days in which the patients took their NUC medication during the given period [17]. In this study, adherence was assessed every 3 months and data from the last 30 days were used as an approximation of the patient's medication behaviour during the 3-month period covered by each questionnaire [18,19]. Patients who indicated they did not miss a single dose of HBV medication during the last 30 days were considered to have perfect adherence.

Virological response was assessed by monitoring serum HBV DNA every 3–6 months. Serum HBV DNA was quantified by real-time polymerase chain reaction assays, COBAS TaqMan HBV (Roche Diagnostics, Indianapolis, IN, USA) with a lower limit of detection of 29 IU/mL. When VBT was detected, serum HBV DNA was retested after 1–3 months and antiviral drug-resistance mutation was tested in those with confirmed VBT. Antiviral drug-resistance mutations were determined by direct sequencing as described previously [20].

VBT was defined as an increase in serum HBV DNA by ≥ 1 $\log_{10}$ above nadir or 10 times the lower limit of detection in patients who had undetectable HBV DNA previously, while on treatment. Confirmed VBT was defined as the persistence of VBT on repeat test at least 1 month later. GR was defined as the detection of signature mutations associated with resistance to the HBV medication the patient was receiving.

Statistical analyses

Continuous variables were expressed as mean ± SD, or median and range. Categorical variables were expressed as number and percentage. Mann–Whitney's test was used to compare continuous variables, while Fisher's exact test was used for categorical data. In all cases, comparisons were two-tailed, and a P-value of <0.05 was considered statistically significant. The data analyses were performed using SPSS software version 18 (SPSS, Chicago, IL, USA).

RESULTS

A total of 159 patients with chronic hepatitis B receiving NUC were seen during the study period. Thirty-three patients were excluded for the following reasons: not fluent in English ($n = 15$), impaired renal function requiring dose adjustment of HBV medication ($n = 6$), decompensated liver disease or transplantation for CHB ($n = 4$), immunosuppression

requiring HBV prophylaxis (n = 3), HIV or hepatitis C virus co-infection (n = 5) and mental disability (n = 2). Thirteen patients declined participation and the most common reasons cited were not wanting to disclose their data (n = 4) and not having enough time to complete the questionnaire (n = 5).

Baseline characteristics of patients

A total of 111 patients were enrolled; 73.9% were men, and the mean age was 47.7 ± 13.1 years. Approximately, half (57.7%) were Asian. Almost half of the patients (42.3%) had a postgraduate degree, 39.7% were professionals and approximately 40% of the patients reported an annual household income of more than $100 000 USD (Table 1).

The mean duration of known HBV infection was 13.3 ± 8.2 years. More than half (56.7%) of the patients had received prior HBV treatment. A variety of treatment regimens were used with 84 patients receiving NUC monotherapy and 27 NUC combinations. The mean duration of the current HBV treatment regimen was 36.7 ± 32 months; 23.4% of patients had been on the current HBV treatment for <1 year, while 15.3% had been on the current treatment for more than 5 years. Most of the patients (80%) had private insurance that covered their HBV medication, and the median copayment per month was $20 (range, $0–360) (Table 2).

Table 1 Demographic and socioeconomic data of patients at enrolment

Characteristics	n = 111
Age (years)	
Mean ± SD	47.7 ± 13.1
Median (range)	49 (19–73)
Gender (male)	82 (73.9)
Race	
Caucasian	40 (36)
Asian	64 (57.7)
African American	4 (3.6)
Other	3 (2.7)
Marital status	
Single	31 (27.9)
Married	76 (68.5)
Divorced	4 (3.6)
Place of birth	
USA	42 (37.8)
Asia	58 (52.3)
Other	11 (9.9)
Education	
Some high school or high school graduate	16 (14.4)
Some college or college graduate	48 (43.3)
Postgraduate degree	47 (42.3)
Occupation	
Student	10 (9)
Not in workforce or homemaker	23 (20.7)
Managers, officials, technical or skilled labour	34 (30.6)
Professional	44 (39.7)
Annual household income (USD)	
≤20 000	17/107 (15.9)
20 001–60 000	30/107 (28.0)
60 001–100 000	18/107 (16.8)
>100 000	42/107 (39.3)

Results expressed as number (%) or mean ± SD unless specified otherwise.

Table 2 Medical history and HBV treatment at enrolment

Characteristics	n = 111
Duration of known HBV infection (years)	
Mean ± SD	13.3 ± 8.2
Previous HBV treatment	
None	48 (43.3)
1 regimen	24 (21.6)
≥2 regimens	39 (35.1)
Payment for HBV medication	
Private insurance	88/110 (80)
Medicare/medicaid	13/110 (11.8)
Own money	2/110 (1.8)
Other	7/110 (6.4)
Copay (USD/month)	
Mean ± SD	36.9 ± 58.6
Median (range)	20 (0–360)
Other chronic illness	
None	64 (57.7)
1 disease	24 (21.6)
≥2 diseases	23 (20.7)
*Number of prescribed oral pills per day**	
None	41 (37)
1 pill	21 (18.9)
≥2 pills	49 (44.1)
Current HBV medication	
Lamivudine	9 (8.1)
Adefovir	7 (6.3)
Entecavir	45 (40.6)
Telbivudine	1 (0.9)
Tenofovir	22 (19.8)
Truvada	16 (14.4)
Other combination	11 (9.9)
Duration of current HBV treatment (months)	
Mean ± SD	36.7 ± 32
Median (range)	26 (3–181)

Results expressed as number (%) or mean ± SD unless specified otherwise. *Not including HBV medications.

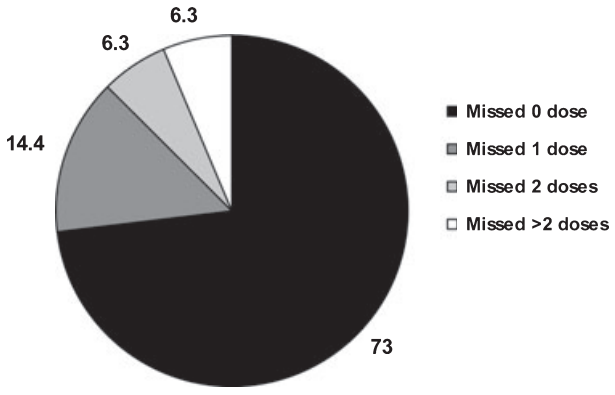

Fig. 1 Adherence at enrolment based on self-reported questionnaire (n = 111). Pie diagram showing the per cent of patients who missed 0, 1, 2 or >2 doses of hepatitis B virus nucleos(t)ide analogue during a 30-day period prior to enrolment.

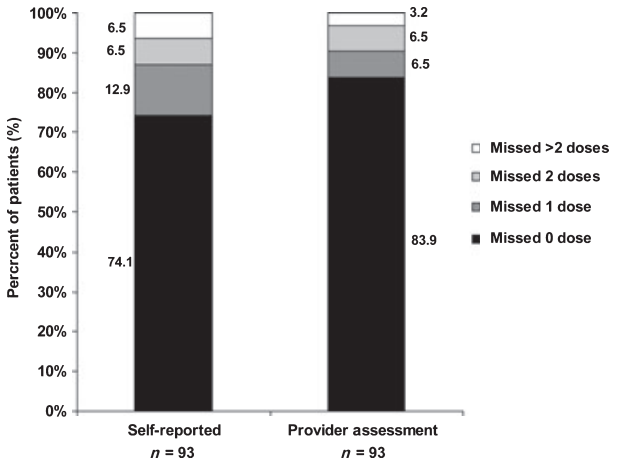

Fig. 2 Comparison of adherence based on self-reported confidential questionnaire and healthcare provider assessment (n = 93). Columns showing the per cent of patients who missed 0, 1, 2 or >2 doses of hepatitis B virus nucleos(t)ide analogue during a 30-day period prior to enrolment.

Adherence to HBV medication

At enrolment, the mean adherence rate based on self-reporting was 98.2 ± 3.8%. Eighty-one (73%) patients reported that they did not miss any dose of HBV medication in the last 30 days (perfect adherence), while 14.4%, 6.3% and 6.3% reported that they missed their HBV medication on 1, 2 and more than 2 days, respectively, in the last 30 days (Fig. 1). Of the seven patients who missed their HBV medication more than 2 days, three missed their HBV medication on 3 days, one on 4 days, two on 5 days and one on 6 days.

Adherence rates remained stable during the course of the study. At the time when the study was closed, 96, 86, 71 and 41 patients had completed the follow-up questionnaire at months 3, 6, 9 and 12, respectively, and the rates of perfect adherence at these time points were 78.1%, 80.2%, 77.5% and 73.2%, respectively. Thirty-seven patients completed all five questionnaires through month 12, 15 patients reported perfect adherence on each occasion, eight patients reported less than perfect adherence through enrolment and perfect adherence on all (n = 3) or some questionnaires during follow-up (n = 5), while 12 patients reported perfect adherence initially and less than perfect adherence on ≥1 questionnaires during follow-up. Only two patients reported less than perfect adherence on all occasions.

Adherence rates reported in confidential questionnaire vs adherence rates reported to healthcare provider

At enrolment, 93 (83.8%) patients had documentation of adherence assessment by their healthcare providers. Seventy-eight patients reported to their healthcare provider that they did not miss any dose of HBV medication in the last 30 days but only 69 (88.5%) of these 78 patients reported perfect adherence in the confidential questionnaire (Fig. 2).

Reasons for missing HBV medication

At enrolment, 30 patients reported that they missed their HBV medication on ≥1 days during the last 30 days. The most common reasons why HBV medication was missed were forgetfulness (n = 20) and travelling away from home (n = 4).

Factors associated with perfect adherence at study enrolment

Patients with perfect adherence at enrolment were more likely to be men and to be older and had a higher annual household income (Table 3). Race, education, occupation, duration of known HBV infection, type of current HBV medication, history of previous treatment, type of health insurance, copayment for HBV medication, presence of comorbid medical conditions and number of other prescribed oral pills were not different between the two groups.

Correlation between adherence rate and virological breakthrough and genotypic resistance

At enrolment, 85 patients had been on the current HBV treatment regimen for >12 months. Of these, 45 of 63 (71.4%) patients with 100% adherence and 17 of 22 (77.3%) patients with <100% adherence had undetectable HBV DNA (P = 0.78).

Eighty (72.1%) patients completed all three questionnaires at months 0, 3 and 6. Forty-six (57.5%) patients reported perfect adherence on all three questionnaires (group 1), 18

Table 3 Characteristics of patients with and without perfect adherence at enrolment

Variables	Adherence rate < 100%	Adherence rate = 100%	*P* value
Total patients	30	81	
Age (years)			
Mean ± SD	43.2 ± 12.5	49.4 ± 13.1	***0.02***
Gender (male)	16 (53.3)	66 (81.5)	***0.006***
Race			
Caucasian	9 (30)	31 (38.3)	0.27
Asian	17 (56.6)	47 (58)	
African American	2 (6.7)	2 (2.5)	
Other	2 (6.7)	1 (1.2)	
Education			
Postgraduate degree	9 (30)	38 (46.9)	0.13
Other	21 (70)	43 (53.1)	
Occupation			
Professional	9 (30)	35 (43.2)	0.51
Other	21 (70)	46 (56.8)	
Annual household income (USD)			
<20 000	7 (23.3)	10/77 (13)	***0.04***
20 001–60 000	9 (30.0)	21/77 (27.3)	
60 001–100 000	6 (20)	12/77 (15.6)	
More than 100 000	8 (26.7)	34/77 (44.1)	
Duration of known hepatitis B virus (HBV) infection (years)			
Mean ± SD	11.7 ± 6.7	13.8 ± 8.7	0.36
Other chronic illness			
None	21 (70)	43 (53.1)	0.13
≥1 disease	9 (30)	38 (46.9)	
*Number of oral pills per day**			
None	12 (40)	29 (35.8)	0.79
≥1 pill	18 (60)	52 (64.2)	
Previous HBV treatment			
None	14 (46.7)	34 (42)	0.51
≥1 regimen	16 (53.3)	47 (58)	
Duration of current HBV treatment (months)			
Mean ± SD	35.2 ± 29.5	37.3 ± 33	0.94
Type of insurance			
Private insurance	21/29 (72.4)	67 (82.7)	0.11
Other	8/29 (27.6)	14 (17.3)	
Copay (USD/month)			
Mean ± SD	29.3 ± 41.8	39.7 ± 63.9	0.29

Results expressed as number (%) or mean ± SD unless specified otherwise. *Not including HBV medications. Variables that were statistically significant are given in bold.

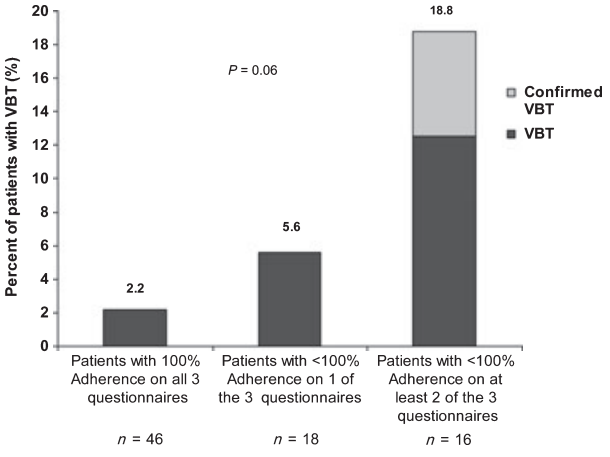

Fig. 3 Correlation between medication adherence and occurrence of virological breakthrough (VBT). Data shown for 80 patients who completed all three questionnaires at enrolment, month 3 and month 6.

reported <100% adherence on one of the three questionnaires (group 2), and 16 reported <100% adherence on at least two of the three questionnaires (group 3). During the first 6 months after enrolment, VBT was observed in one patient (2.2%) in group 1, one patient (5.6%) in group 2 and 3 patients (18.8%) in group 3 ($P = 0.06$) (Fig. 3). Of the three patients who experienced VBT in group 3, two had confirmed VBT on retesting. VBT was not confirmed in the third patient in group 3 and the two patients in groups 1 and 2. None of the patients with VBT had evidence of antiviral drug-resistance mutations by direct sequencing. Serum HBV DNA decreased in all five patients during continued treatment with the same medication.

DISCUSSION

In this study, we found that adherence to NUCs in patients with CHB being treated in an outpatient hepatology clinic was very high. Based on responses to the confidential questionnaire, the mean adherence rate was 98% and 73% of patients reported that they did not miss a single dose of medication during the past 30 days. The adherence rate based on patients' report to healthcare providers was even higher (99%), and 84% of patients indicated that they did not miss a single dose of medication during the past 30 days. These adherence rates were higher than the 87.8% adherence rate among existing patients in our previous study of a nationwide prescription refill database [16].

Several factors may explain the very high rate of adherence to HBV NUCs observed in this study. First, adherence based on self-reporting may be inflated. Studies that compared medication adherence based on self-reporting with adherence assessed by other methods such as medication electronic monitoring systems and pill count have found adherence rates based on self-reporting to be 10–30% higher [21]. In this study, we found that when adherence was assessed simultaneously, patients reported higher rates of adherence to their healthcare providers than what they recorded in a confidential questionnaire. Another reason for the high adherence rate in this study may be related to the fact that most of our patients were highly educated, affluent, with good health insurance and low copayment for their medications. Other studies have shown that low educational level, lack of prescription coverage and high copayment for medications are associated with lower adherence rate to medications [22–25]. A third possible explanation for the high adherence rate is that our patients were seen in a tertiary clinic and monitored by an experienced team of hepatologists, physician assistants and nurses who are committed to the care of patients with viral hepatitis. Indeed, 78% of our patients indicated that their healthcare providers played a primary role in reminding them the importance of taking their HBV medications daily.

Comparison of the patients with and without 100% adherence found that patients with perfect adherence were older, more likely to be men and had higher annual household income. Several studies also found a higher rate of adherence to HIV treatment, statins and antihypertensive drugs among older patients [16,26–28]. Older patients may be more concerned about preserving their health or they may be aware that they are at higher risk of complications from chronic HBV infection. Several previous studies revealed that women had higher adherence to medications than men [28–30]. One potential explanation why we found a higher adherence rate among men is that many of our patients may have been aware that men with chronic HBV infection have a higher risk of developing cirrhosis and hepatocellular carcinoma.

The adherence rate to NUC remained high during the study period (mean adherence rate 97.7–99.1%), although we acknowledge that only 64% and 36.9% of the cohort had been followed to months 9 and 12, respectively. Of the 80 patients who completed the questionnaire at enrolment, month 3 and month 6, 46 (58%) reported 100% adherence on all three questionnaire, while 16 (20%) reported that they missed at least one dose in two of the three questionnaire. The latter patients were more likely to experience VBT than those with consistently perfect adherence (19% *vs* 2%, $P = 0.05$). Testing for GR failed to reveal any antiviral drug-resistance mutation and serum HBV DNA decreased in all patients during continued treatment, supporting the notion that the VBTs were secondary to nonadherence to NUC. These data highlight the importance of educating patients on the importance of adherence to HBV NUC and the need for programmes to assist patients in remembering to take their medications. Our findings also underscore the importance of confirmation of VBT by retesting serum HBV DNA and/or confirmation of GR before changing treatment. The association between transient treatment interruption and viral rebound and antiviral drug resistance has also been reported

in the studies of patients receiving non-nucleoside reverse transcriptase inhibitor-based treatment for HIV infection [31–33].

This study has several limitations. First, the number of patients studied was small. Second, the study population was highly educated and affluent. Third, patients who were not fluent in English were excluded. Fourth, the patients were managed in a tertiary liver centre by an experienced team with a long-standing interest in hepatitis B treatment. Thus, the results in this study may be a best-case scenario and cannot be generalized to other patient populations. Finally, objective methods to verify adherence reported in the questionnaire and healthcare provider assessment were not used. Nevertheless, this is the first study to examine adherence to HBV NUC in a cohort of more than 100 patients with CHB in clinical practice and its association with the occurrence of VBT. In addition to patient self-reporting using a confidential questionnaire, adherence was simultaneously assessed by healthcare providers in clinic. Furthermore, adherence was assessed serially over a period of up to 12 months in a subgroup of patients.

In conclusion, adherence to NUC therapy in our patients with CHB was very high but self-reporting of adherence to healthcare providers may be overestimated. Patients who maintained 100% adherence to NUC therapy had a trend towards a lower rate of VBT. Our data highlight the importance of education on medication adherence to improve the effectiveness of HBV treatment in clinical practice and provide insights into how adherence may be augmented.

STATEMENT OF INTERESTS

Authors' declaration of personal interests

Watcharasak Chotiyaputta, Chanunta Hongthanakorn, Kelly Oberhelman and Tracy Licari have no declaration of personal interests. Robert J Fontana – Speaker's bureau: Gilead, Genetech; Grant/Research Support: Bristol-Myers Squibb; Consulting: GlaxoSmithKline. Anna SF Lok Consulting – Gilead Sciences, GlaxoSmithKline, Roche, and Bristol-Myers Squibb; Grant/Research Support: Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Schering-Plough, Roche, and Innogenetics.

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REFERENCES

1 Chang TT, Gish RG, de Man R *et al.* A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. *N Engl J Med* 2006; 354: 1001–1010.
2 Lai CL, Shouval D, Lok AS *et al.* Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B. *N Engl J Med* 2006; 354: 1011–1020.
3 Lai CL, Gane E, Liaw YF *et al.* Telbivudine versus lamivudine in patients with chronic hepatitis B. *N Engl J Med* 2007; 357: 2576–2588.
4 Marcellin P, Heathcote EJ, Buti M *et al.* Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. *N Engl J Med* 2008; 359: 2442–2455.
5 Westland CE, Yang H, Delaney IV, WE *et al.* Week 48 resistance surveillance in two phase 3 clinical studies of adefovir dipivoxil for chronic hepatitis B. *Hepatology* 2003; 38: 96–103.
6 Hadziyannis SJ, Tassopoulos NC, Heathcote EJ *et al.* Adefovir dipivoxil for the treatment of hepatitis B e antigen-negative chronic hepatitis B. *N Engl J Med* 2003; 348: 800–807.
7 Marcellin P, Chang TT, Lim SG *et al.* Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. *N Engl J Med* 2003; 348: 808–816.
8 Bramley TJ, Gerbino PP, Nightengale BS, Frech-Tamas F. Relationship of blood pressure control to adherence with antihypertensive monotherapy in 13 managed care organizations. *J Manag Care Pharm* 2006; 12: 239–245.
9 Bouchard MH, Dragomir A, Blais L, Berard A, Pilon D, Perreault S. Impact of adherence to statins on coronary artery disease in primary prevention. *Br J Clin Pharmacol* 2007; 63: 698–708.
10 Dragomir A, Cote R, Roy L *et al.* Impact of adherence to antihypertensive agents on clinical outcomes and hospitalization costs. *Med Care* 2010; 48: 418–425.
11 Palella Jr FJ, Delaney KM, Moorman AC *et al.* Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med* 1998; 338: 853–860.
12 Paterson DL, Swindells S, Mohr J *et al.* Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med* 2000; 133: 21–30.
13 Nachega JB, Hislop M, Dowdy DW, Chaisson RE, Regensberg L, Maartens G. Adherence to nonnucleoside reverse transcriptase inhibitor-based HIV therapy and virologic outcomes. *Ann Intern Med* 2007; 146: 564–573.
14 Harrigan PR, Hogg RS, Dong WW *et al.* Predictors of HIV drug-resistance mutations in a large antiretroviral-naive cohort initiating triple antiretroviral therapy. *J Infect Dis* 2005; 191: 339–347.
15 Maggiolo F, Ravasio L, Ripamonti D *et al.* Similar adherence rates favor different virologic outcomes for patients treated with nonnucleoside analogues or protease inhibitors. *Clin Infect Dis* 2005; 40: 158–163.

16 Chotiyaputta W, Peterson C, Ditah FA, Goodwin D, Lok AS. Persistence and adherence to nucleos(t)ide analogue treatment for chronic hepatitis B. *J Hepatol* 2011; 54: 12–18.
17 Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med* 2005; 353: 487–497.
18 Walsh JC, Mandalia S, Gazzard BG. Responses to a 1 month self-report on adherence to antiretroviral therapy are consistent with electronic data and virological treatment outcome. *AIDS* 2002; 16: 269–277.
19 Lu M, Safren SA, Skolnik PR *et al.* Optimal recall period and response task for self-reported HIV medication adherence. *AIDS Behav* 2008; 12: 86–94.
20 Degertekin B, Hussain M, Tan J, Oberhelman K, Lok AS. Sensitivity and accuracy of an updated line probe assay (HBV DR v.3) in detecting mutations associated with hepatitis B antiviral resistance. *J Hepatol* 2009; 50: 42–48.
21 Liu H, Golin CE, Miller LG *et al.* A comparison study of multiple measures of adherence to HIV protease inhibitors. *Ann Intern Med* 2001; 134: 968–977.
22 Amico KR, Konkle-Parker DJ, Cornman DH *et al.* Reasons for ART nonadherence in the Deep South: adherence needs of a sample of HIV-positive patients in Mississippi. *AIDS Care* 2007; 19: 1210–1218.
23 Jackson JE, Doescher MP, Saver BG, Fishman P. Prescription drug coverage, health, and medication acquisition among seniors with one or more chronic conditions. *Med Care* 2004; 42: 1056–1065.
24 Doshi JA, Zhu J, Lee BY, Kimmel SE, Volpp KG. Impact of a prescription copayment increase on lipid-lowering medication adherence in veterans. *Circulation* 2009; 119: 390–397.
25 Maciejewski ML, Bryson CL, Perkins M *et al.* Increasing copayments and adherence to diabetes, hypertension, and hyperlipidemic medications. *Am J Manag Care* 2010; 16: e20–e34.
26 Donnelly LA, Doney AS, Morris AD, Palmer CN, Donnan PT. Long-term adherence to statin treatment in diabetes. *Diabet Med* 2008; 25: 850–855.
27 Mantel-Teeuwisse AK, Goettsch WG, Klungel OH, de Boer A, Herings RM. Long term persistence with statin treatment in daily medical practice. *Heart* 2004; 90: 1065–1066.
28 Caro JJ, Salas M, Speckman JL, Raggio G, Jackson JD. Persistence with treatment for hypertension in actual practice. *CMAJ* 1999; 160: 31–37.
29 Marentette MA, Gerth WC, Billings DK, Zarnke KB. Antihypertensive persistence and drug class. *Can J Cardiol* 2002; 18: 649–656.
30 Kane SV, Cohen RD, Aikens JE, Hanauer SB. Prevalence of nonadherence with maintenance mesalamine in quiescent ulcerative colitis. *Am J Gastroenterol* 2001; 96: 2929–2933.
31 Parienti JJ, Das-Douglas M, Massari V *et al.* Not all missed doses are the same: sustained NNRTI treatment interruptions predict HIV rebound at low-to-moderate adherence levels. *PLoS ONE* 2008; 3: e2783.
32 Parienti JJ, Massari V, Descamps D *et al.* Predictors of virologic failure and resistance in HIV-infected patients treated with nevirapine- or efavirenz-based antiretroviral therapy. *Clin Infect Dis* 2004; 38: 1311–1316.
33 Oyugi JH, Byakika-Tusiime J, Ragland K *et al.* Treatment interruptions predict resistance in HIV-positive individuals purchasing fixed-dose combination antiretroviral therapy in Kampala, Uganda. *AIDS* 2007; 21: 965–971.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1: Initial questionnaire.

Table S2: Subsequent questionnaire.

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