

**FACTORS ASSOCIATED WITH NON-ADHERENCE TO  
HEPATITIS B VIRUS ANTI-VIRAL THERAPY**

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## **Factors associated with non-adherence to hepatitis B virus anti-viral therapy**

### **Abstract**

Background: Hepatitis B virus (HBV) anti-viral therapy has the potential to reduce the burden of HBV-related liver disease by suppressing HBV deoxyribonucleic acid (DNA) replication to undetectable levels, reducing the progression of liver fibrosis and reducing the risk of hepatocellular carcinoma (HCC) development. Treatment outcomes and long-term benefits require adherence to medication regimens. This study aimed to identify the prevalence and factors associated with non-adherence to anti-viral therapy. Methods: A cross-sectional survey of patients receiving HBV anti-viral therapies was conducted in three Sydney hospitals. Participants were asked to complete an online questionnaire. Logistic regression was used to assess the associations between non-adherence (defined as missing more than one day of medication in the last 30 days) and demographic, socio-economic, disease, treatment, health-care-system and individual-related factors. Results: Of the 277 participants, 66 (23.8%) were non-adherent, missing a mean 1.7 days of medication (SD 4.8) in the last 30 days. In multivariate analysis, non-adherent behaviour declined with age (OR 0.9 95% CI 0.97-0.99,  $p < 0.013$ ). Participants who reported having no established routine to take their medication (OR 5.0, 95%CI 1.4–17.4,  $p < 0.012$ ) and having inadequate health literacy (OR 2.7, 95%CI 1.3-5.5,  $p < 0.007$ ) were more likely to be non-adherent. Conclusion: Almost a quarter of participants in the current study were non-adherent. Adherence is potentially modifiable through person-centred education, collaborative models of patient care and interventions designed to improve health literacy and establish medication routines. Findings have the potential to improve health service delivery to patients at risk of non-adherence to HBV anti-viral therapy.

**Key words:** medication adherence, chronic HBV, non-adherence, routine, health literacy, viral hepatitis

Chronic hepatitis B virus (HBV) infection is a global health problem [1, 2] with an estimated 213,000 (range 175,000–253,000) Australians living with the condition [3]. HBV anti-viral therapy has the potential to reduce the burden of HBV-related liver disease [1] by suppressing HBV deoxyribonucleic acid (DNA) replication to undetectable levels, reducing the progression of liver fibrosis [4] and reducing the risk of hepatocellular carcinoma HCC development [4, 5]. Treatment outcomes and long term benefits require adherence to medication regimens.

Adherent behaviour is influenced by a complex interaction of five factor domains: social and economic factors, health care system factors, disease/condition-related factors, treatment-related factors and individual factors [6]. In most chronic disease settings adherent behaviour is well researched [7-9], however adherence research in HBV has a very short history with the first study published in 2011 [10]. To date, HBV adherence studies have provided sketchy descriptions of adherent behaviour. The eight studies published to date report that between 66% and 73% of participants were 100% adherent [10-13], 66.2% of participants were >95% adherent [14], and 70% of participants were >80% adherent [15] to their HBV medications. Two of these studies report a mean adherence rate of 99.4% over 12 months [16] and 87.8% (SD19.1%) over a three-year period [10]. A decline in adherent behaviour over time was described in one study with rates decreasing from 98.1% at three months to 81.4% after 12 months [12, 17]. This pattern of behaviour was more common in people new to therapy than in longer-term patients [10]. To date, seven studies have investigated why people miss HBV anti-viral therapy. Studies have explored limited demographic, socio-economic, disease and treatment-related factors. Only one recently published study investigated the relationship between adherent behaviour and individual-related factors [15], and another study explored the relationship between health-care-system related factors and non-adherence [14] (Table 1). Improving HBV anti-viral therapy

adherence rates and optimising treatment outcomes requires that clinicians gain a deeper understanding of the barriers to, and facilitators of, adherence in this patient population.

**Using an established evidence base definition for non-adherence** [18] this study aimed to 1) measure the frequency of self-reported non-adherence to HBV anti-viral medications in the last 30 days and 2) identify predictors of self-reported non-adherence.

## **Methods**

### *Population and sample*

A multi-site cross-sectional survey of 277 people receiving oral HBV anti-viral therapies was undertaken in 2013–2014 in three tertiary hospitals in Sydney, Australia. Patient medical records were reviewed to determine eligibility and the first author attended each hospital clinic per week (4-6 hours) during the recruitment period. People who were unable to speak English, reported a history of hepato-cellular carcinoma or had been taking anti-viral therapy for  $\leq$  six months were excluded from the study. All eligible participants (n=398) were approached individually by the first author and invited to participate. Close to a third of participants approached (n=121, 30.5%) declined to participate (Figure 1). A sample size of 300 patients was determined to provide adequate power to detect binary covariates that increase the odds of non-adherence by about twofold.

Lead approval for the study was granted by St Vincent's Hospital Research Office, Sydney (HREC/13/SVH/218) and site-specific approval by three hospital sites. Participants were asked to sign a written consent to complete a de-identified online adherence based questionnaire administered by the first author.

### *Measures*

The questionnaire was designed using a secure online data collection platform SurveyGizmo. At the time of the study, there were no validated HBV adherence-based questionnaires. Therefore, we designed our data collection tool based on data from our formative qualitative work exploring factors influencing adherent behaviour [19]. The questionnaire included demographic (8 questions), treatment-related (7 questions), and disease-related (6 questions) factors and asked whether medications had been missed in the last 30 days and if ever missed, and the number of days missed. A recall time of 30 days was selected (Chesney et al. 2000). Health-care-system related (12 questions) factors included measuring the quality of communication between a clinician (defined as doctor or registered nurse) and a patient using a validated questionnaire adapted from the University of Washington Quality of Communication (QOC) questionnaire [20]. Validated tools were used to assess Individual-related (8 questions) factors such as treatment and disease knowledge, readiness to start treatment and disclosure. Participants were also asked to complete questions to measure health literacy (six questions) [21], psychological distress and depression (10 questions) [22] and the use of alcohol and other drugs (six questions) [23].

### **Non-adherence definition**

**An evidence-based definition was determined by the authors in a previous study [18]. Combining collected cross-sectional survey data from this cohort and participant's results of virological testing determined a clinically relevant and evidence-based definition of non-adherence [18]. Various combinations of missed days and never missed days were analysed to ascertain the level of adherence and/or non-adherence most strongly associated with virological breakthrough (defined as "greater than 1 log<sub>10</sub> [10-fold] above nadir after achieving virological response during continued treatment") [24]. Missing more than one**

**day of medication in the previous 30 days was most strongly associated with virological breakthrough (RR 8.3, OR 10.2 95%CI 3.1-33.8  $p \leq 0.001$ , ROC= 0.76) and was adopted as the definition of non-adherence for subsequent analyses. [18].**

#### *Data management and analyses*

Participant responses were entered directly into a secure online software tool used to develop questionnaires and store survey data via a secure link. At the end of study recruitment the dataset was downloaded into a master database for cleaning and recoding. All analyses were undertaken in STATA 12.0 (StataCorp, College Station, TX, USA). Exploratory analyses were conducted to inspect variable distributions.

Demographic and socio-economic factors, treatment-related factors, HBV disease-related factors and individual-related factors were assessed for univariate associations with non-adherence.

Non-adherence was defined as missing more than one day of medication in the last 30 days.

Variables significantly associated with non-adherence in univariate analyses ( $p < 0.05$ ) were included in a multivariable logistic regression model. Variables were considered independent predictors of non-adherence if  $p < 0.05$  in the final multivariate model. Multivariate models described were assessed using the Hosmer-Lemeshow goodness of fit test based on 10 categories. The Hosmer-Lemeshow goodness of fit tests were not statistically significant ( $p = 0.91$ ) indicating no evidence of poor fit to the data.

#### **Results**

Demographic characteristics, socio-economic-related factors, disease-related factors and HBV treatment-related factors of the 277 participants are presented in Table 2. **Virology results are presented in Figure 2.** Health-care related factors were explored including patient education,

hospital infrastructure, pharmacy access, quality of clinician-patient communication.

Approximately two-thirds of participants (n=193, 69.7%) reported receiving pre-treatment education regarding the need to take their medication daily (n=191, 68.9%) and about the risks of missing or stopping anti-viral therapy (n=144, 51%). Forty-three participants (15.5%) said that they had difficulty collecting medication and had run out, primarily due to the limited operating hours of their hospital-based pharmacy. The quality of communication between themselves and their clinician at their last appointment rated a mean 7.8 (SD 1.3) where a score of ten was perceived as the best imaginable quality of communication.

Our study found that individual-related factors were varied. Less than half the sample (n=128, 46.2%) had adequate health literacy (defined as a score of 4-6) slightly higher than Australian data [25]. Almost all participants (n=259, 93.5%) reported knowledge that anti-viral therapy should be taken at the same time daily and 227 (82%) were aware of HBV treatment benefits. In contrast, less than half (n=116, 41.6%) of the participants were aware that treatment cessation could trigger an elevation of liver enzymes and/or HBV DNA replication and a third (n=103, 37.2%) indicated that they did not know how long their therapy would last. A small percentage (n=3, 1%) of participants perceived anti-viral therapy to be toxic, deliberately missed medication to manage treatment related side effects or reported the need to frequently take a break from medication within the last 30 days. Participants (n=225, 81.2%) said that they had disclosed their HBV status with the majority (n=217, 96.4%) reporting that they felt supported by their family and friends. Three quarters (n=208) of the sample reported that they felt ready to start anti-viral therapy. Psychological distress or depression was reported by a small number of participants (n=38, 13.7%) with 36 participants (13.7%) reporting clinically insignificant symptoms. Moderate and severe related symptoms were unrelated to HBV. The use of alcohol and other

drugs in this sample was lower than expected with one fifth of participants reported lifetime alcohol consumption (n=55, 19.8%) and a small number of participants reported a history of tobacco consumption (n=30, 10.8%), cannabis (n=4, 1.5%) or other illicit drug use (n=5, 1.8%).

### *Self-reported non-adherence*

Of the 277 participants, 66 (23.8%) were non-adherent, reporting that they had missed more than one day of anti-viral medication in the last 30 days. **Slightly more than a third of participants (n=102, 36.8%) reported that they had never missed a day of HBV anti-viral therapy.** The mean numbers of single and consecutive days of anti-viral therapy missed are reported in Table 3. One in ten patients (30, 10.8%) had missed clinical appointments in the three or six months prior to questionnaire completion.

### *Factors associated with non-adherence to HBV anti-viral therapy*

Demographic characteristics, disease-related, treatment-related health care system- and individual-related factors associated with non-adherence in univariate and multivariate analyses are shown in Table 4. Controlling for factors significant at  $p < 0.05$  in univariate analysis, multivariate analysis indicated that age (OR 0.9, 95% CI 0.97-0.99,  $p < 0.013$ ) was associated with non-adherence. Participants who reported having no established routine to take their medication (OR 5.0, 95%CI 1.4–17.4,  $p < 0.012$ ) and those who had inadequate health literacy (OR 2.7, 95%CI 1.3-5.5,  $p < 0.007$ ) were significantly more likely to be non-adherent.

## **Discussion**

To the best of our knowledge, this is the first study to comprehensively assess the associations between risk factors and non-adherence to HBV anti-viral therapy using an evidence based



definition [18]. Previous studies have investigated limited demographic, treatment and disease-related factors. Using a comprehensive questionnaire and an evidence-based definition of non-adherence (defined as missing more than one day in the last 30 days), we found that close to a quarter of participants reported non-adherence to HBV medications in the last 30 days. This is a lower rate than that reported in previous studies which defined adherence as >80% to 100% of medication taken in the last month [11, 14, 15]. Younger age and not having an established routine to take medication and inadequate health literacy were independently associated with non-adherence. The slightly lower prevalence of non-adherent behaviour here is possibly related to changes in clinical practice and Australian HBV clinical guidelines during the course of this study [24]. Recent published research highlighted the prevalence of non-adherence to HBV antiviral therapy [10, 12], and raised an awareness that non-adherence is associated with virological breakthrough [26, 27]. Non-adherent behaviour to these medications is concerning given the risk of developing drug-related resistance, virological breakthrough and hepatic flares [28, 29]. Various factors have been associated with patients' decision to miss medication in other chronic disease settings including attitudes towards medication, inflexible clinic appointments, poor clinician-patient communication [30], illness beliefs, patient knowledge [31], and younger age [32, 33]. Laba et al. (2012, 2015) suggests that the intention to miss medication is temporary and potentially reversible; however, these authors cautioned that this depends on the reasons for non-adherence, and if barriers to adherence prove intractable, non-adherent behaviour will persist [30, 34].

The current study found that relative decline in medication non-adherence with age was 10% per year. Findings are consistent with qualitative data and with previous studies that describe a relationship between younger age and non-adherence [10, 12, 19]. Indeed in our earlier

qualitative study, non-adherent participants who commenced HBV treatment at a younger age (< 45 years) described a period of transition and adjustment to taking medicine daily. This group of patients described the importance of establishing a routine when treatment commenced [19].

Participants with no established HBV anti-viral medication routine were more than five times more likely to be non-adherent than those who had an established medication routine. This is the first quantitative study to identify the significance of medication routines and the risk that its absence poses for non-adherence to HBV anti-viral therapy. The importance of establishing a medication routine has been previously reported in one HBV study [14] and is consistent with the broader adherence literature [35-39]. Saunders et al. (2013) described the unique nature of individual medication-taking behaviour and suggests the use of environmental cues to choreograph a set routine [40]. Establishing a routine is best made a component of individualised pre-treatment education and ongoing treatment monitoring, and may require the involvement of family members and or carers. Tailoring the use of existing interventions such as pill dispensers or mobile telephone alarms may be sufficient to improve medication adherence. The third factor independently associated with non-adherence in the current study was inadequate health literacy, which was associated with a 2.7-fold increase in the odds of non-adherence. Previous studies have not formally measured health literacy in HBV-affected populations undergoing treatment. Language discordance [14] and ineffective communication between patients and clinicians [19] have been reported to influence adherent behaviour without measuring health literacy as a potential factor contributing to misinterpretation of key health messages. Considering that more than half of the current study population reported less than adequate health literacy and that the HBV-affected population in Australia is composed primarily of migrants from non-English-speaking HBV-endemic countries [41], it is essential that health

care providers are universally responsive to the individual health literacy needs of their patients. An individual's ability to effectively communicate does not necessarily equate to adequate health literacy [42]. The use of appropriate interpreter services may overcome communication barriers and address poor English proficiency however, such strategies will not address health literacy unless clinician's use simple language and omit complex medical jargon.

Medication adherence requires an interaction of several health literacy skills to be able to follow administering instructions and to navigate hospital infrastructure to access treatment and monitoring [41, 43-45]. It is now acknowledged that it is the responsibility of all clinicians to communicate healthcare information in a way that patients and carers understand [25]. Strategies to ensure that patients have understood instructions and how to access services are necessary to limit the risk of non-adherence. The universal use of techniques such as teach-back is a positive approach to addressing and promoting the health literacy needs of all patients and limits the barriers associated with low health literacy [46-48]. Core teach-back components include the use of simple language and avoidance of medical jargon. In addition, establishing a clinical environment conducive to building trust and collaborative relationships is recommended to enable patients and their families to disclose low literacy levels [49].

Our study had several limitations. Financial constraints prevented the translation of PICF and the study questionnaire into other languages, which limited the inclusion of participants who were unable to read or speak English. The study was reliant on participant self-report and as such is also subject to social desirability and recall bias [50], however the use of an experienced clinician interviewer not directly involved in patients' care probably reduced the influence of social desirability. The current study has several strengths and is the largest study to date to assess a comprehensive range of factors and their potential association with self-reported non-

adherence to HBV anti-viral therapies. Demographic characteristics and multiple variables from the WHO five domains of adherence [6]: socio-economic, disease, treatment, health-care-system- and individual-related factors such as health literacy, psychological distress and patient knowledge not previously assessed in relation to HBV, were examined in the current study. Numerous studies have described medication adherence in chronic disease settings over the last two decades, yet few studies have explored non-adherence to HBV anti-viral therapies. This study adds substantially to the limited knowledge about HBV medication adherence and identifies ways to improve nursing practice and key factors to be targeted by interventions designed to improve adherence. Focused nursing education and adherence counselling may be required to commence at a younger age to minimise the risk of developing drug related resistance or other drug cessation related complications. In addition, recommendations to improve adherence include designing a set medication routine in collaboration with patients pre-treatment and the universal use of techniques to effectively communicate with patients, such as avoiding medical jargon and the use of simple language. Such strategies should enable the delivery of key treatment and adherence-related messages optimising treatment related response and health outcomes.

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### **Declaration of Conflict of Interest**

The first author has no conflicts of interest to declare.

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Boards

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Study	N	Follow-up	Adherence Definition	Adherence rate	Assessment tool	Variables associated with non-adherence	P value	Variables associated with adherence	P value
Chotiyaputta et al., 2011(12)	11,100	1 year	>90% of days medication was stored by patient/ time on treatment	Persistence Mean 87.8%	Pharmacy refill claims	Age <45 years New patient LAM	<0.001 <0.001 <0.001		
Chotiyaputta et al., 2012(181)	111	1 year	100%	Mean 98%	Questionnaire			Older age Male Income	<0.020 <0.006 <0.040
Sogni et al., 2012 (330)	190	6 months	100%	61%	Questionnaire Visual analogue	Recent initiation	<0.085		
Hilleret et al., 2011 (327)	47	4 years	Undetected serum ADV	N/A	ADV serum level	Younger age High viral load HBeAg positive	N/A		
Giang et al., 2012 (329)	80	6 months	>95%	66%	Questionnaire Visual analogue	Taking other medications Language discordance	<0.039 <0.040		
Peng et al., 2015 (332)	211	1 year		Mean 96.3%-99.4%	Pill count	ETV LAM	<0.010 <0.020	Female Naïve Telbivudine	<0.001 <0.001 <0.001
Van Vlerken et al., 2015(331)	136	4 months	80%	Mean 85%  70% (>80% adherent)	Sensemedic dispenser	Younger age  Poor medication attitude	0.180  0.120		

Table 1: Studies of HBV adherence and non-adherence

Table 2: Demographic, socio-economic, HBV treatment and HBV disease-related factors

Characteristics (n=277)	N	%	Mean (SD, median, range)
<b>Gender</b>			
Male	170	61.4	
Female	107	38.6	
<b>Age</b>			46.5 (12.7,47, 20-79)
<b>Country of birth by WHO region</b>			
Africa	15	6.16	
Europe	19	5.69	
South East Asia	23	9.48	
Western Pacific	207	74.4	
Australia	13	4.3	
<b>Years living in Australia</b>			19 (11.5,18,6mths-52)
<b>Preferred language spoken at home</b>			
English	74	26.7	
Other language	203	73.3	
<b>Education</b>			
≤ 10 years	63	22.7	
>10 years	102	36.9	
University degree or higher	112	40.4	
<b>Income per annum</b>			
≤\$25,000 (AUS)	130	46.9	
>\$25,000 (AUS)	147	53.1	
<b>Current anti-viral therapy</b>			
ETV	111	40.1	
TDF ,	95	34.3	
TDF & LAM	15	5.4	
ADV &LAM	9	5.1	
LAM	14	3.2	
Don't know	33	11.9	
<b>Number of HBV regiment changes regiment</b>			1 .4 (0.8, 1, 1-5)
<b>Pill burden (other than HBV)</b>			
No other medications	132	47.7	
>1 other medication			
<b>Years diagnosed with HBV</b>			15.9 (12, 14,1-79)
<b>HBeAg status</b>			
Negative	163	60.4	
Positive	70	25.9	
Borderline neg/pos	1	0.4	
Not reported in last 12 months	36	13.3	
<b>Self-reported degree of liver fibrosis</b>			
Cirrhosis	40	14.4	
No cirrhosis			
Don't know	64	23.2	

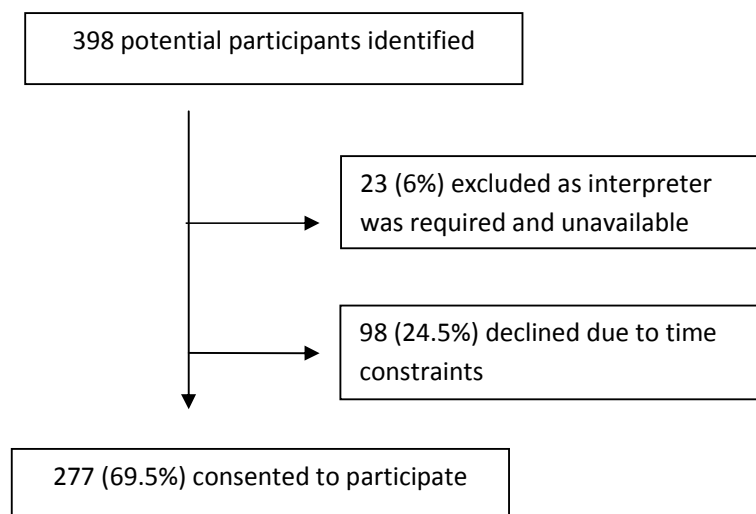
Table 3: Self-reported non-adherence to HBV anti-viral therapy (N=277)

<b>Adherence</b>	<b>N</b>	<b>(%)</b>	<b>Mean (SD, median, range)</b>
<b>Missed more than one day of HBV anti-viral therapy</b>			
No	211	(76.1)	
Yes	66	(23.8)	
<b>Mean number of days missed in the last 30 days</b>			
Single days			1.7 (4.8, 0, 0–30)
Consecutive days			5.4 (7.6, 2, 2–30)

Table 4: Demographic, disease, treatment, health-care-system and individual-related factors associated with non-adherence in univariate analyses (n=277)

Adherence related factors	Non-adherent participants N	(%)	Univariate analysis			Multivariate analysis		
			OR	95%CI	p value	OR	95%CI	p value
Age (per year)			0.9	0.9-1.0	0.036	0.9	0.9-1.0	*0.013
HBeAg status (229)								
Negative	34/159	21.3	1.0					
Positive	24/70	34.2	1.9	1.0–3.5	0.040	1.8	0.9–3.7	0.100
Pre-treatment education from clinician								
No	28/84	33.0	1.0					
Yes	38/193	19.6	0.5	0.3-0.9	0.010	0.9	0.3-2.7	0.915
Adherence education (daily dose)								
No	30/86	34.8	1.0					
Yes	36/191	18.8	0.4	0.2-0.8	0.004	1.06	0.3-2.0	0.470
Education about risk of stopping medication								
No	42/133	31.5	1.0					
Yes	24/144	16.6	0.4	0.2-0.8	0.004	0.5	0.3-2.7	0.260
Problem collecting medication from pharmacy								
No	50/234	21.4	1.0					
Yes	16/43	37.2	2.1	1.1-4.3	0.030	1.9	0.8-4.5	0.106
Pre-treatment education from clinician								
No	28/84	33.0	1.0					
Yes	38/193	19.6	0.5	0.3-0.9	0.010	0.9	0.3-2.7	0.915
Knowledge: Benefits of treatment								
Medication will control the hepatitis	48/227	21.0	1.0					
Medication will cure my hepatitis	5/17	29.4	1.5	0.5–4.6	0.430	0.9	0.2–3.8	0.890
I don't know	13/33	39.0	2.4	1.1–5.2	0.030	1.2	0.5–3.4	0.630
Established routine/set time								
Yes	53/259	20.5	1.0					
No it doesn't matter	13/18	72.0	10.1	3.4–29.5	≤0.001	5.0	14-17.4	*0.012
Health literacy								
Adequate health literacy	19/128	14.8	1.0					
Possibly or high likelihood of low health literacy	47/149	31.5	2.6	1.4–4.8	0.001	2.7	1.3–5.5	*0.007
Alcohol consumption (n=41)								
≤14 standard drinks per week	14/41	34.1	1.0					
>14 standard drinks per week	27/41	65.8	2.4	1.1–5.5	0.030	2.4	0.8–6.8	0.09

Figure 1: Flow chart of recruitment



**Figure 2. Flowchart of study sample virology results**