FACTORS ASSOCIATED WITH HEPATITIS B VIRUS VIROLOGICAL BREAKTHROUGH

Background: Little is known about non-adherence to Hepatitis B virus (HBV) therapy. This study aimed to investigate the relationship between self-reported missed days of anti-viral therapy and HBV virological breakthrough and factors associated with virological breakthrough.

Methods: A cross-sectional survey of 211 HBV patients receiving oral anti-viral therapies was undertaken at three tertiary hospitals in Sydney, Australia. Associations between 0 to > 6 missed days in the last 30 days and virological breakthrough (defined as > 10-fold rise in serum HBV DNA above nadir or after achieving virological response in the last 12 months) were examined. Logistic regression analyses determined the number of missed days most strongly associated with virological breakthrough and the associated factors. We report odds ratios and relative risks.

Results: Of the 204, 32 participants (15.6%) had quantifiable HBV DNA levels (> 20 IU/mL); 15 (46.8%) of them experienced virological breakthrough. Participants reported never missing medication (n=130, 63.7%) or missing one day (n=23, 11.3%), >one day (n=23, 11.3%), 2-6 days (n=15, 7.3%) and >6 days (n=13, 6.4%). The most discriminating definition of non-adherence was missing > one day of medication (RR=8.3; OR=10.2, 95%CI: 3.1-33.8, ROC 0.76). Factors independently associated with virological breakthrough included non-adherence (OR=9.0, 95%CI: 2.5–31.9) diagnosed with HBV ≤ 14 years (OR=5.3, 95%CI: 1.0–26.2) and age ≤ 47 years (OR=5.4, 95%CI: 1.1–26.9).

Conclusion: Results provide an evidence-based definition of non-adherence to inform clinical practice and provide a basis for key patient education messages. Closer monitoring of groups at risk of viral breakthrough is required.

Key words: adherence, anti-viral therapy, hepatitis B virus, non-adherence, virological breakthrough, risk factors

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Chronic hepatitis B virus (HBV) is a global health problem affecting 300–400 million people worldwide [1, 2] and an estimated 213,000 (range 175,000–253,000) Australians [3]. Individuals chronically infected with HBV are at risk of developing liver-related sequelae including liver cirrhosis [4, 5], hepato-cellular carcinoma (HCC), end-stage liver disease and liver failure [6-8]. Treatment of chronic HBV can reduce the burden of HBV-related liver disease [1]. HBV anti-viral therapies effectively suppress HBV DNA replication, reducing the progression of liver fibrosis [9] and reducing the risk of HCC development [9, 10]. However, non-adherence or abrupt cessation of HBV therapy enables HBV DNA replication and virological breakthrough, and may culminate into a hepatic flare [11] that can lead to liver decompensation and death [12, 13].

Virological breakthrough is defined by the American Association for the Study of Liver Disease (AASLD) and the European Association for the Study of the Liver (EASL) as a "greater than 1 log10 (10-fold) increase above nadir after achieving virological response, during continued treatment" (p. 9 and p.176) [14, 15]. Clinical guidelines from Asia Pacific regions are similar, however evidence of virological breakthrough must be supported by two consecutive samples one month apart" [16, 17].

Previous studies have described rates of virological breakthrough ranging between 0% and 55.8% [11, 18-21], with lower rates reported in patients receiving second generation medications such as entecavir (ETV) and tenofovir (TDF) [21]. Hongthanakorn et al. (2011) were the first to highlight that non-adherence to HBV anti-viral medications posed a problem [11]. The authors retrospectively reviewed 112 medical records and found that only 49% of participants who had virological breakthrough had evidence of genotypic resistance, suggesting that non-adherence

was contributing to virological breakthrough [11]. Subsequent studies have confirmed these findings by concurrently measuring virological breakthrough and non-adherence [18, 20, 22-24], but none provided a consistent definition for non-adherence that is evidence-based. One of the most challenging issues in the field of medication adherence research is the use of varied definitions and arbitrary cut-off points to define adherence to therapies. Our study aimed to investigate the relationship between self–reported missed days of anti-viral therapy in the last 30 days and virological breakthrough (defined as a greater than 10-fold rise in serum HBV DNA above nadir or after achieving virological response in the last 12 months).

Methods

Selection and Description of Participants

Adults aged 18 years or older who were being prescribed oral anti-viral therapy for chronic HBV infection were invited to participate in a cross sectional survey at three tertiary hospital sites in Sydney, Australia. People who reported a history of HCC, were unable to speak English or had been taking anti-viral therapy for ≤ six months were excluded.

Participants were asked to provide written informed consent to complete a questionnaire and to consent to their clinic providing copies of HBV DNA viral load and pathology results collected over the previous year (blood tests were performed routinely as standard care, and were not requested specifically for this study). Human Research Ethics Committee (HREC) approval for the study was granted by St Vincent's Hospital Research Office (HREC/13/SVH/218) and site-specific approvals granted by each of the three hospital sites.

Technical Information

The primary endpoint for this study was to investigate the relationship between self–reported missed days of anti-viral therapy in the last 30 days and virological breakthrough, defined as a greater than 10-fold rise in serum HBV DNA above nadir or after achieving virological response in the last 12 months. Secondary endpoint aimed to identify which factors are associated with virological breakthrough.

An online questionnaire for this study was built following a previous qualitative study that identified factors that influenced adherent behaviour (in press). The questionnaire included demographic, treatment and disease-related questions and asked whether medications had been missed in the last 30 days and if ever missed, the number of days missed. Participant responses were entered directly into SurveyGizmo using an iPad computer. SurveyGizmo is a secure online software tool used to develop questionnaires and store survey data via a secure link until study completion. Data were de-identified as per lead HREC requirements. All questionnaires were matched to virology results (HBV DNA viral load) linked by site number, study code, age (not date of birth, as per HREC requirement), gender and date of completion of questionnaire. Virological tests were requested by outpatient liver-clinic staff as per standard of care at each site. HBV DNA was detected by reverse transcription polymerase chain reaction (PCR) using COBAS® AmpliPrep/COBAS® TaqMan® HBV Test (linear range 20 to 170,000,000).

Statistics

Although 277 participants were recruited, this analysis excluded participants with potential confounding factors (n=66) known to effect HBV DNA viral load suppression, such as receiving anti-viral therapy for <18 months (n=15), participants' lack of knowledge of the name of their medication (n=33), had been prescribed lamivudine (LAM) alone or with adefovir (ADV) (n=14) (4). Excluding participants with these

potential confounders was an attempt to remove bias in order to determine a true association between missed medication and virological breakthrough. Sensitivity analyses were also performed including all participants and produced very similar results (not presented here).

The initial analysis assessed the association between the number of missed days of anti-viral therapy and virological breakthrough. Several definitions of non-adherence were assessed, including one to six single days missed and two to six consecutive days missed in the last 30 days. Associations between non-adherence and virological breakthrough were assessed as odds ratios (OR) using logistic regression. This method is a valid way of assessing associations in cross-sectional studies, and has the advantage that other studies have used this method, with estimates of associations across studies in the form of odds ratios being directly comparable. An estimate of the relative risk (RR) corresponding to the estimated odds ratio and prevalence of virological breakthrough in adherent patients was also provided. Sensitivity and specificity, and ROC curves, were used to determine the definition of adherence that best predicted viral breakthrough [25].

Results

Demographic characteristics of participants

The 211 participants were predominantly men (n=127, 60.2%) and were, on average, 45 years old (range: 23–77, mean 45.5, SD 12.2). More than 95% (n=264, 95.3%) of participants were migrants. This group had lived in Australia for a median of 17.5 years (range: 6 months–51 years, mean 17.5 years, SD 11.2) and came from six geographical regions.

HBV–treatment-related factors

Anti-viral therapy had been prescribed for a median of 4 years (range: 18 months–30 years, mean 5.1, SD 4.2), with a median of one regimen change since treatment

initiation (range 1–5, mean 1.4, SD 0.8). Anti-viral therapies included ETV (n=107, 50.7%) and TDF (n=89, 42.2%), or a combination of TDF and LAM (n=15, 7.1%). Consistent use of traditional Chinese medicines in combination with anti-viral therapy was reported by 32 participants (15.2%).

HBV disease-related factors

The median time since participants were diagnosed with chronic HBV was 12 years (range 6 months–63, mean 14.8, SD 10.9) with 40 (19%) reporting a HBV-related illness prior to their diagnosis. Receiving a diagnosis of cirrhosis was reported by 32 participants (15% of the study sample). Virology results were available for 204 (96.7%) of the study sample. Undetectable HBV DNA levels were reported in less than half of the study sample (Figure 1). Thirty-two participants (15.6%) had quantifiable HBV DNA levels (> 20 IU/mL), with 15 of these participants (46.8%) experiencing virological breakthrough (Figure 1). Virology results for the remaining 17 participants revealed varied patterns of decreasing, fluctuating or plateaued viral loads.

Self-reported non-adherence

Of the 204 participants who had virology results and had completed an adherence questionnaire, 130 (61.6%) reported never missing medication in the last 30 days. Of the remaining participants, 74 (35.1%) reported missing a single day of anti-viral therapy or more.

Relationship between days of medication missed and virological breakthrough

Associations between never missed, missed single or consecutive days of treatment (more specifically, a single day, more than one day, more than two days, more than three days, more than four days and more than six days in the last 30 days) and virological breakthrough were investigated to determine the level of non-adherence most strongly associated with virological breakthrough. The results of logistic regression models involving these measures of missed days and virological

breakthrough for 204 participants (96.7%) are shown in Table 1. The best discriminating definition of non-adherence was missing more than one day of medication, with a relative risk (RR) of 8.3 (OR 10.2, 95%CI 3.1-33.8, p≤0.001, ROC 0.76) and sensitivity and specificity of detecting the outcome of 73.3% and 78.8% respectively. Although other potential definitions of non-adherence were associated with virological breakthrough, all reported lower ROC values, indicating poorer discrimination (Table 1). Missing more than one day of anti-viral therapy in the last 30 days was reported by 51 participants, with 11 (21.5%) of those participants reporting virological breakthrough. These findings provided the basis for the definition of non-adherence as *missing more than one day of anti-viral therapy in the past 30 days*. This definition was used in subsequent analyses.

Factors associated with virological breakthrough

Factors independently associated with virological breakthrough include medication non-adherence (OR 9.0, 95%CI 2.5–31.9.3, p≤0.001), diagnosed with HBV ≤ 14 years (OR 5.3, 95%CI 1.0–26.2, p<0.04) and age ≤ 47 years (OR 5.4, 95%CI 1.1–26.9, p<0.04) (Table 2).

Discussion

HBV DNA was detectable (> 20 IU/mL) in 32 participants (15.6%), with 15 (46.8%) of these experiencing virological breakthrough. Various combinations of missed days were analysed to determine the definition of non-adherence most strongly associated with virological breakthrough (missing more than one day of medication in the previous 30 days). Predictive factors associated with virological breakthrough were missing more than one day of anti-viral medication in the last 30 days, age ≤ 47 years and diagnosed ≤ 14 years previously.

Demographic characteristics

Although participants of this sub-study were not selected to form a sample representative of the Australian patients with chronic HBV, their demographic characteristics closely reflect the epidemiology of Australians living with chronic HBV and undergoing anti-viral therapy [26-29]. Clinicians' consistent use of international HBV treatment guidelines [14, 30] is the most likely reason for the similarity of demographic characteristics between this sub-study sample and across previous HBV treatment-based studies. Most participants migrated from HBV-endemic countries [31, 32], in particular, Western Pacific countries such as Tonga, and also China [28, 29]. The over-representation of participants from the Western Pacific region is not surprising given recent patterns of migration to Australia [28] and the considerable burden of HBV disease within the Western Pacific region [31].

HBV anti-viral therapy response

Suppression of HBV DNA to undetectable levels, or to detectable but unquantifiable levels ≤20 IU/mL, was reported by 172 participants (84.3%). The rate of viral suppression reported here is comparable to treatment response rates reported in previous studies [33-36] and a population study review of a heterogeneous sample [19]. Of the remaining 32 (15.6%) participants with detected and measurable HBV DNA, 15 participants experienced virological breakthrough. This accounts for 7% (n=15/204) of the total study population reporting virological breakthrough and is comparable to previous studies of patients having a history of varied treatment experience [11, 19, 21, 37]. Most studies attribute viral breakthrough to genotypic resistance; however studies have indicated that it is possible other factors such as medication non-adherence plays a role [11]. Clinical guidelines provide recommendations for managing viral breakthrough and potential hepatic dysfunction [14, 30].

Relationship between days of medication missed and virological breakthrough

Although few studies have described the reasons why people are non-adherent to HBV anti-viral therapies, recent reports have acknowledged the relationship between non-adherence and virological breakthrough [18, 22, 23, 38]. Development of an understanding of adherent behaviour in HBV-affected populations has been hindered by insufficient research, varied methods/tools used to measure adherence, and different definitions of adherence. The inconsistent use of adherence definitions is particularly problematic, as findings from the few existing studies are not easily comparable. Several studies have defined HBV medication adherence by selecting arbitrary cut-offs ranging from 80% to 100% to define adherence [24, 37, 39-41] or have adopted the definition of 95% used in HIV/AIDS settings [39]. The current study assessed various combinations of any missed days and consecutive missed days as predictors of virological breakthrough to determine the range of days most associated with virological breakthrough. This allowed determination of an evidence-based definition of non-adherence. The identified association between missing more than one day of therapy and virological breakthrough is broadly similar to that reported in two previous studies. Chotiyaputta et al. (2012) found that patients who reported missing at least one day of anti-viral therapy two or three times in six months were likely to experience virological breakthrough ($p<0.05$). Kamezaki et al. (2013) described a similar relationship, finding virological breakthrough in four patients receiving ETV who had taken <90% of their prescribed anti-viral therapy ($p\leq0.001$). Adherence research in HBV is relatively new, with the first known study published in 2011 [38]. The evidence-based definition of non-adherence adopted by the current study enables future studies to adopt a consistent definition, and provides for comparisons of adherence and risk factors across studies. Findings from the current study also have implications for informing clinical practice in that they revealed that any number of days missed in the past 30 days significantly magnified the risk of virological breakthrough. This finding

provides key information to be delivered during patient education and adherence counselling.

Factors associated with virological breakthrough

Missing more than one day of anti-viral therapy, age ≤47 years and having HBV diagnosed for ≤14 years were significant predictors of virological breakthrough. There is growing clinical evidence [40, 41] and clinician acknowledgement [19, 42] that non-adherence compromises treatment response. Missing more than one day of anti-viral therapy was associated with virological breakthrough in multivariate analyses. The findings suggest that there is a need to raise the definition of adherence to over 95% in a 30-day period. It is also necessary to reinforce the importance of medication adherence to prevent virological breakthrough. Previous studies have demonstrated the relationship between non-adherence and virological breakthrough in the absence of clinical factors such as drug resistance [18, 23, 43]. Increasing clinician and patient awareness and improving education is imperative to achieve higher levels of adherent behaviour.

In this study, participants aged ≤47 years were more likely to experience virological breakthrough, consistent with findings reported in two previous studies [20, 22]. Both of these studies also described non-adherence as a significant covariate associated with virological breakthrough. As previously discussed, few studies have described the effect of age or length of years since HBV diagnosis as independent predictors of viremia [20]. In this research, participants who had been diagnosed with HBV infection for ≤14 years were more likely to have viral breakthrough. Although it is difficult to interpret this finding, the number of years since HBV diagnosis may be a surrogate indicator of other factors such as duration of treatment, age or adherent behaviour. This study is, as far as can be ascertained, the largest study to date to measure the association between the numbers of self-reported missed days of HBV anti-viral

therapy and virological breakthrough. Confounding factors reported to impact on treatment response and virological breakthrough such as the use of first-generation anti-viral therapies were excluded from the sample for this sub-study in order to more robustly estimate the true effects of missed medication.

The limitations of this study include the retrospective collection of virology and serology results three, six and twelve months prior to study interviews, and the lack of genotypic resistance testing to exclude drug-related resistance cases. In addition, self-reported data are subject to recall and social desirability bias, especially in relation to studies of treatment adherence conducted in clinical settings. While it is possible that non-adherence was under-ascertained, this would most likely lead to under-estimation of associations between non-adherence and virological breakthrough rather than over-estimation. Furthermore, any under-ascertainment would affect all the definitions of non-adherence assessed. For these reasons, the finding that low levels of non-adherence (more than one day missed in the last 30 days) were most strongly associated with virological breakthrough is believed to be robust.

Finally, this study produced an evidence-based definition of non-adherence that can be used in future HBV adherence research, enabling consistency and better comparisons across studies. In addition, this definition informs clinical practice, in that patients reporting missing more than a single days' medication in the previous month are at increased risk of virological breakthrough, and provides the basis for key messages to be delivered during patient education.

In conclusion, missing more than one day of treatment and younger age were associated with virological breakthrough and detectable HBV DNA. Therefore, providing consistent adherence counselling and patient education to achieve adherence is vital to avoid drug resistance and hepatic flares associated with HBV virological breakthrough.

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Table 1 Association between self-reported non-adherence and virological breakthrough (N=204)

Self–reported adherence in the last 30 days	Participants reporting, N (%)	Virological breakthrough (n)	OR (95% CI)	RR	p value	ROC	Sensitivity %	Specificity %
Never missed	130 (63.7)	4	Reference group					
Single day missed	74 (36.2)	11	5.5 (1.6–17.9)	4.8	≤0.001	0.70	73.0	66.6
>1 missed days	51 (25.0)	11	10.2 (3.1–33.8)	8.3	0.001	0.76	73.3	78.8
>2 missed days	28 (13.7)	7	7 (2.3–21.2)	5.5	≤0.001	0.67	46.7	88.9
>3 missed days	23 (11.2)	7	9.4 (3.0–29.4)	6.8	≤0.001	0.69	46.7	91.5
>4 missed days	19 (9.3)	6	9.0 (2.7–29.2)	6.5	≤0.001	0.66	40.0	93.1
>6 missed days	13 (6.3)	5	11.3 (3.1–40.9)	7.3	≤0.001	0.64	33.3	95.7
>2 consecutive missed days	38 (18.6)	8	6.0 (2.0–17.9)	6.1	0.001	0.68	53.3	84.1
>4 consecutive missed days	16 (0. 8)	7	17.5 (5.1–59.0)	10.3	≤0.001	0.70	46.6	95.2
>5 consecutive missed days	14 (0.7)	6	15 (4.3–52.0)	9.1	≤0.001	0.67	40.0	95.0
>6 consecutive missed	13 (0.6)	6	17.3 (4.8–62.3)	9.7	≤0.001	0.68	40.0	96.3

Table 2. Factors associated with virological breakthrough (N=204)

Variable	No. of participants who report non-adherence	(%)	Univariate analysis			Multivariate analysis		
			OR	95% CI	p value	OR	95% CI	p value
Gender								
Male	13/122	(10.6)	1.0					
Female	2/82	(14.6)	0.2	0.04–0.9	0.043	0.32	0.06–1.6	0.172
Age								
>47	2/94	(0.02)	1.0					
≤47	13/110	(11.8)	6.1	1.3–28.0	0.019	5.4	1.1–26.9	0.040
HBeAg status								
HBeAg negative	7/124	(5.6)	1.0					
HBeAg positive	5/57	(0.9)	1.6	0.5–5.12	0.436			
Cirrhosis								
No cirrhosis	12/174	(6.8)	1.0					
Cirrhosis	5/57	(8.7)	1.5	0.4–5.6	0.550			
Number of years diagnosed								
> 14	12/174	(6.8)	1.0					
≤14	3/30	(10.0)	6.3	1.3–28.0	0.017	5.3	1.0–26.2	0.040
Medication name								
ETV	4/92	(4.3)	1.0					
TDF or combination (TDF & LAM)	11/112	(1.0)	2.3	0.73–7.7	0.147			
Number of regime changes								
Never changed	12/136	(8.8)	1.0					
≥ one change	3/68	(0.4)	0.5	0.12–1.7	0.260			
Missing ≥1 day AV therapy								
No	4/153	(0.3)	1.0					
Yes	11/51	(21.5)	10.2	3.1–33.8	≤0.001	9.	2.5–31.9	0.001

Table 3 Thirty-two cases of detectable HBV DNA viral load > 20 IU/mL at -12, -6 and -3 months and on the day of survey completion.[1]

	- 12 months	- 6 months	-3 months	Day of survey
1			**101658**	**170000000**
2			**0**	**143**
3	**0**			**13081**
4	**0**			**152**
5	168910		63219	83
6	**0**	**0**	**0**	**13081**
7	0	0		29
8	3460	15700		22600
9	**0**	**0**		**2890**
10	**151000**	**9080**		**215000**
11	**0**	**0**		**20900**
12	**0**	**0**		**2890**
13	**0**	**0**		**3320**
14		8150		6060
15		47200		1370
16	170 000 000	4080000		2190
17	119	39119	0	27
18	**23**	**56**		**12091**
19	348	313	324	336
20	0	0		24
21	0	0	0	39
22	2150000	20 200	24 300	110 00
23		**0**		**5040**
24	**276301**		**4020**	**13035131**
25	602	553		604
26	170000000			1690254
27	**0**	**0**		**62500**
28	170000000	383000		2060
29	439	91		31
30		170000000		806
31		20138	3277	7057
32	**154000**	**4640**		**85500**

[1] 15 virological cases highlighted in bold text

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