

## FACTORS ASSOCIATED WITH NON-ADHERENCE TO HEPATITIS B VIRUS ANTIVIRAL THERAPY

Anum Khan, Asif Farooq, Abdul Rehman Arshad, Farrukh Saeed

Pak Emirates Military Hospital/National University of Medical Sciences (NUMS) Rawalpindi Pakistan

### ABSTRACT

**Objective:** To assess the adherence to antivirals in Hepatitis B Virus (HBV) infected patients and to determine various social and demographic factors which can have an impact on it.

**Study Design:** Cross-sectional study.

**Place and Duration of Study:** Department of Gastroenterology, Pak Emirates Military Hospital Rawalpindi, from Jan to Mar 2019.

**Methodology:** Patients on oral anti-viral agents for hepatitis B virus infection were enrolled from outdoor clinics using consecutive sampling technique. Medication adherence was assessed using the 4-item Modified Morisky Score Questionnaire. Data was also collected about different variables that could potentially affect compliance, such as age, gender, education, residence, total number of pills prescribed for each day, travelling time to hospital, attendant's company, adverse effects of treatment, presence of co-morbid conditions, patients' knowledge regarding importance of adherence and whether they followed any particular routine in taking medicines.

**Results:** There were 127 patients having mean age of  $47.80 \pm 14.54$  years. Out of these, 20 (15.75%) were not adherent to treatment. Patients not following a fixed drug-dosing schedule, patients not aware of the significance of good drug compliance and residents of urban areas were more likely to have lesser compliance to treatment.

**Conclusion:** Majority of our patients were compliant to treatment for chronic hepatitis B infection. This was more likely to be the case amongst those following a fixed drug-dosing schedule, having an awareness of significance of adherence to medication and residents of rural areas.

**Keywords:** Chronic Hepatitis B, Medication Non-adherence, Patient Compliance.

**How to Cite This Article:** Khan A, Farooq A, Arshad AR, Saeed F. Factors Associated with Non-Adherence to Hepatitis B Virus Antiviral Therapy. Pak Armed Forces Med J 2021; 71(6): 2065-2069. Doi: <https://doi.org/10.51253/pafmj.v6i6.2983>

---

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<https://creativecommons.org/licenses/by-nc/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

---

### INTRODUCTION

Hepatitis B Virus (HBV) infection is a major public health problem, with almost 240 million people affected worldwide.<sup>1</sup> Infection rates are rising rapidly in developing countries like Pakistan, due to lack of vaccination and awareness about the disease in the general public and health care workers. Chronic HBV infection is a dynamic disease with various phases. The virus itself is not directly cytopathic to the hepatocytes. Rather, it is the immune response to HBV that causes liver injury, leading to cirrhosis, hepatic decompensation and increased risk of hepatocellular carcinoma (HCC). HBV infected patients with immune active disease (raised serum alanine transaminase, necro inflammation on histology or cirrhosis) or/and a high viral load are recommended to be treated with antivirals. Treatment is usually long-term and variable. It depends on HBeAg status, viral load and presence of cirrhosis. The aim is not virus eradication, but viral load

suppression by inhibiting replication to prevent liver injury and extra hepatic complications of the disease. Nucleotide Analogues (NAs), namely entecavir and tenofovir, are the recommended oral antivirals with a good efficacy and safety profile. Treatment with antivirals, however, doesn't eliminate risk of HCC and thus regular surveillance for HCC is essential.<sup>2</sup>

Effective viral suppression as well as the prevention of virological breakthrough and resistance to drugs require good adherence to antiviral therapy. Patients need to be educated about this and the importance of good compliance needs to be reinforced repeatedly. People from our part of the world are different from the Western population in many aspects such as level of education and cultural background. Interpolating data from international studies may therefore not be a good choice. The rationale of the study is that since local data is required to guide therapy in our patients therefore this study was designed to assess the level of non-adherence to anti-viral drugs in HBV infected patients and various social and demographic factors that can have an impact on it. This would in turn help

---

**Correspondence:** Dr Anum Khan, Resident Medicine, Pak Emirates Military Hospital, Rawalpindi Pakistan

Received: 23 Jun 2019; revision received: 10 Feb 2020; accepted: 25 Feb 2020

us improve treatment outcomes by focusing more on patients with higher risk of missing their medications.

**METHODOLOGY**

This cross-sectional study was carried out at the Gastroenterology Department, Pak Emirates Military Hospital Rawalpindi, from January to March 2019. Approval of ethics review committee of the institute was obtained beforehand (Letter number A/28 dated 30<sup>th</sup> November 2018). A minimum sample size of 114 patients was calculated taking non-compliance rates of up to 8% a total population size of 250 (as estimated by hepatitis B patient records held at our department), alpha value of 0.05 and confidence interval of 95%.<sup>3</sup>

Patients visiting the Gastroenterology OPD were enrolled using consecutive sampling technique, subject to informed consent. **Inclusion Criteria:** Patients who were receiving oral Entecavir/Tenofovir for at least 30 days and who could understand and communicate in Urdu or English were included. **Exclusion Criteria:** Patients who did not give informed consent or those with a communication barrier were excluded. Medication adherence was assessed using Modified Morisky Score (MMAS-4) question-naire, which was translated in Urdu.

Patients were asked four questions directly during the clinical encounter by the examining physician and their responses were noted down. Data was also collected about different socio-demographic and treatment-related variables that could potentially affect compliance, such as age, gender, education, residence, total number of pills prescribed for each day, travelling time to hospital, attendant’s company, adverse effects of treatment, presence of co-morbid conditions, patients’ knowledge regarding importance of adherence and whether they followed any particular routine in taking medicines.

Data were analysed using Statistical Package for the Social Sciences (SPSS) version 23. Scores of 3 or 4 on MMAS- 4 indicated good compliance, whereas lesser scores were consistent with poor compliance. Univariate and bivariate logistic regression analysis were applied to determine the relationship of compliance with different possible predictive factors. The *p*-value ≤0.05 was considered significant.

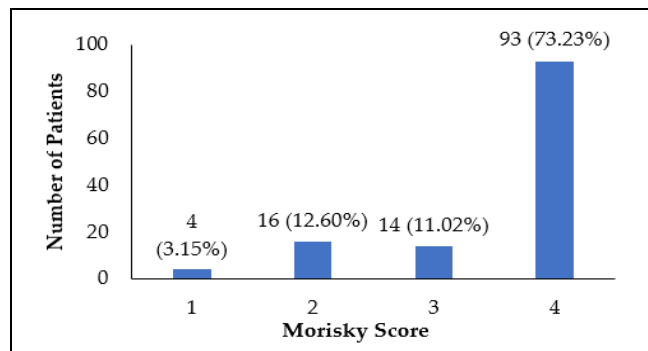
**RESULTS**

This study included 127 patients having mean age of 47.8 ± 14.54 years. Other baseline characteristics are shown in Table-I. MMAS-4 score of ≤2 (poor adherence) was observed in 20 (15.75%) patients

**Table-I: Baseline characteristics.**

| Parameters                               | n (%)                    |             |
|--|--------------------------|-------------|
| Gender                                   | Male                     | 109 (85.83) |
|  | Female                   | 18 (14.17)  |
| Education                                | Matric & above           | 70 (55.12)  |
|  | Below matric             | 57 (44.88)  |
| Residence                                | Urban                    | 86 (67.72)  |
|  | Rural                    | 41 (32.28)  |
| Transport                                | Personal                 | 17 (13.39)  |
|  | Public                   | 110 (86.61) |
| Attendant                                | Present                  | 41 (32.28)  |
|  | Not present              | 86 (67.72)  |
| Adverse effects                          | Yes                      | 28 (22.15)  |
|  | No                       | 99 (77.95)  |
| Awareness of Adherence                   | Yes                      | 93 (73.23)  |
|  | No                       | 34 (26.77)  |
| Drug dosing routine                      | Yes                      | 107 (84.25) |
|  | No                       | 20 (15.75)  |
| Income (Mean ± SD)                       | 24.42 ± 17.15 (Rs x1000) |             |
| Travelling time to hospital, (Mean ± SD) | 140.25 ± 131.07 minutes  |             |
| Duration of illness (Mean ± SD)          | 37.63 ± 53.88 months     |             |
| Duration of treatment (Mean ± SD)        | 14.54 ± 15.93 months     |             |
| Number of pills taken daily (Mean ± SD)  | 2.22 ± 1.74              |             |

(Figure). Patients not following a fixed drug-dosing



**Figure: Distribution of morisky scores.**

schedule were almost eighteen times more likely to be non-compliant to medications. Patients not aware of the significance of good drug compliance were three and a half times more likely to be non-compliant and those who resided in urban areas were three and a half times more likely to be less compliant to treatment as shown in Table-II. None of the other variables had a statistically significant association with non-adherence.

**DISCUSSION**

Various studies have been carried out in Pakistan regarding the prevalence, screening, vaccination, perception, preventive practices and treatment of hepatitis B infection but to the best of our knowledge,

**Table-II: Factors predictive of non-adherence to treatment.**

| Parameter                                      | Univariate Analysis |                 | Multivariate Analysis |                    |                 |
|--|---------------------|-----------------|-----------------------|--------------------|-----------------|
|  | OR (95% CI)         | <i>p</i> -value | $\beta$               | OR (95% CI)        | <i>p</i> -value |
| Age  | 1.02 (0.98-1.06)    | 0.29            | -                     | -                  | -               |
| Gender*  | 1.08 (0.28-4.14)    | 0.90            | -                     | -                  | -               |
| Education <sup>†</sup>                         | 2.12 (0.76-5.94)    | 0.15            | 0.37                  | 1.45 (0.41-5.06)   | 0.55            |
| Income   | 1.00 (1.00-1.00)    | 0.23            | 0.00                  | 1.00 (1.00-1.00)   | 0.26            |
| Residence <sup>#</sup>                         | 5.16 (1.13- 23.43)  | 0.03            | 1.96                  | 7.10 (1.02-49.15)  | 0.04            |
| Time to Hospital                               | 0.09 (0.99-1.00)    | 0.70            | -                     | -                  | -               |
| Transport <sup>§</sup>                         | 3.74 (1.19-11.71)   | 0.02            | -0.65                 | 0.51 (0.09-2.83)   | 0.44            |
| Availability of attendant <sup>~</sup>         | 1.52 (0.51-4.51)    | 0.45            | -                     | -                  | -               |
| Duration of illness                            | 1.00 (0.99-1.01)    | 0.55            | -                     | -                  | -               |
| Duration of treatment                          | 1.01 (0.98-1.04)    | 0.36            | -                     | -                  | -               |
| No. of pills taken daily                       | 1.03 (0.78-1.34)    | 0.82            | -                     | -                  | -               |
| Adverse effects <sup>@</sup>                   | 1.21 (0.40-3.70)    | 0.72            | -                     | -                  | -               |
| Co- morbid conditions <sup>‡</sup>             | 1.34 (0.49-3.64)    | 0.55            | -                     | -                  | -               |
| Drug- dosing schedule <sup>‡</sup>             | 18.56 (5.88- 58.54) | <0.01           | 2.89                  | 18.02 (4.32-75.03) | <0.01           |
| Awareness of adherence importance <sup>‡</sup> | 5.80 (2.111-15.912) | <0.01           | 1.25                  | 3.52 (1.00-12.32)  | 0.04            |

Reference Category: \*Male, <sup>†</sup>Below matrix, <sup>#</sup>Rural, <sup>§</sup>Public transport, <sup>~</sup>Attendant available, <sup>@</sup>No, <sup>‡</sup>Yes

no data documenting adherence to antiviral treatment in hepatitis B infected patients and predicting factors related to non-adherence in our population has been gathered to-date. Our study showed good compliance in patients, which was positively associated with drug intake routine, knowledge of significance of compliance and rural residence.

Hepatitis B infection has emerged as a crucial and undefiable public health concern. A global systematic review including 101 countries revealed the prevalence in 248 million people in 2010.<sup>4</sup> Another systematic review estimated that there were 7-9 million carriers of hepatitis B virus in Pakistan in 2011.<sup>5</sup> A study done by Ono *et al.* on 403 patients in Japan revealed high chances (96%) of undetectable hepatitis B virus DNA with minimal emergence of resistance (only 0.4%) in nucleotide naive patients who received entecavir continuously over 4 years.<sup>6</sup> The current antiviral agents for HBV cannot achieve the loss of HBsAg or HBsAg sero-conversion.<sup>7</sup> Optimum adherence to therapy is very challenging to achieve in hepatitis B infected patients due to an indefinite period of treatment and the target of maintaining sustained viral suppression instead of viral eradication or cure.<sup>8</sup> The risk of treatment failure, progression of liver disease to uncompensated cirrhosis and HCC, virological breakthrough and emergence of resistant strains due to lack of compliance to antiviral drugs further necessitates optimum adherence.<sup>9-11</sup> Thus, it is pertinent to study various factors that can potentially affect adherence to antiviral drug therapy and by doing so we can address the modifiable factors and make the treatment outcomes more promising.

Evidence-based definition of non-adherence by Shepherd *et al.* that we have adopted has been deter-

mined on the basis of correlation with virological breakthrough (caused by missing drug doses) after reaching virological response during treatment. Thus, non-adherence is "missing more than one day of medication in the previous 30 days".<sup>12</sup>

Patient's self-report of adherence or questionnaires are indirect measures of evaluating medication adherence. We have used the 4 item Morisky Medication Adherence Scale (MMAS-4) which is a validated tool for measuring drug compliance.<sup>13</sup> At present, five nucleos(t)ide analogues are in use for the treatment of chronic hepatitis B infection.<sup>14</sup> Most of our patients were receiving Entecavir (88.2%). The rest were using tenofovir (TDF). These are the first line NUCs recommended by WHO.<sup>15</sup>

On the basis of the evidence-based definition of non-adherence and MMAS-4 score, our study shows that only 15.7% of the patients had self-reported sub-optimal adherence, whereas the vast majority (84.3%) had good compliance to oral antiviral agents. Our results are comparable with other studies. An Australian research on hepatitis B infected patients reported non-adherence in 23.8%, the majority were compliant.<sup>12</sup> Younger age, not following a drug dosing schedule and insufficient health literacy were significantly related to poor anti-viral compliance. Another study reported poor compliance to hepatitis B antivirals in 6-45% of the patients, which was attributed to younger age and frequent change in clinicians.<sup>16</sup> Age, however, did not appear to have any impact on compliance in our patients. This could be because our median age was high (47.8  $\pm$  14.54 years) and very few young individuals were a part of our data. Giang *et al.* found self-reported sub-optimal adherence in 33.8%. 'Forgetful-

ness' had the strongest association (56.25%), while change in daily routine was independently accounted for low compliance in 10.42%.<sup>17</sup> A retrospective analysis by Chotiyaputta *et al.* reported good adherence (55.3%).<sup>18</sup> Compliance is reported to be poor in the Chinese population (51.2% with low adherence).<sup>19</sup>

Many studies reinforce the importance of presence of an established drug intake routine for better adherence to therapy.<sup>20</sup> It is generally believed that fixed drug dosing routines eliminate the chance of forgetting medicine intake. Self-set reminders and family members can encourage patients to be more regular in drug intake. We identified that the patients who received pre-treatment education by their prescribing clinician about the importance of compliance to this treatment and the hazards of omitting doses, showed better adherence as compared to those who did not receive adherence education. Residents of rural areas showed better compliance rates in our population. This was an unusual result when compared to other studies.<sup>19</sup> We do not have a good explanation for this finding. A larger data with equal number of patients from rural and urban areas would be able to identify the impact of residence on medication compliance.

A systemic review and meta-analysis by Ford *et al.* reinforced that 'the most commonly reported barriers to adherence were forgetting (three studies, 81.1%; 95% CI, 68.7-93.5%), limited understanding of the importance of adherence (two studies, 32.3%; 95% CI, 17.2-47.4%), and change to daily routine (two studies, 27.4%; 95% CI, 4.7-50.1%).<sup>21</sup>

Studies have also demonstrated the relationship of adverse drug reactions and increase in pill burden with poor compliance.<sup>17</sup> These factors did not contribute to non-adherence in our patients. NAs have a good safety profile.<sup>22</sup> Only 22.15% patients reported minor and infrequent adverse effects to Entecavir, like gastrointestinal upset, altered taste and body aches. Good adherence to NAs can be attributed to simple dosage, a single pill per day that has negligible adverse effects.<sup>23</sup> Our patients who were using more than one pill per day due to co-existing diseases did not appear to miss the daily dose of antivirals.

#### LIMITATION OF STUDY

Our study has a few limitations. MMAS-4, being subjective, was prone to self-report and recall bias, resulting in over-estimation of adherence. It was difficult to overcome this shortcoming because of absence of any objective marker of compliance for outdoor patients. We did not correlate adherence with treatment

response (HBeAg sero-conversion and viral load) due to limited resources and short duration of the study. All of the patients in this study were receiving medicines free of cost, so the financial impact on compliance could not be evaluated. Compliance is dynamic and our patients were not followed to assess compliance.

#### CONCLUSION

Majority of our patients were compliant to treatment for chronic hepatitis B infection. This was more likely to be the case amongst those following a fixed drug-dosing schedule, having an awareness of significance of adherence to medication and residents of rural areas.

**Conflict of Interest:** None.

#### Author's Contribution:

AK: Direct Contribution, AF: Intellectual contribution, ARA: Intellectual contribution, FS: Intellectual contribution.

#### REFERENCES

- Sarin SK, Kumar M, Lau GM, Abbas Z, Chan HL, Chen CJ, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. *Hepatology* 2016; 10(1): 1-98.
- Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 Hepatitis B guidance. *Hepatology* 2018; 67(4): 1560-1599.
- Ha NB, Ha NB, Chaung KT, Trinh HN, Nguyen HA, Nguyen KK, et al. Similar response to entecavir 0.5 and 1.0 mg in treatment-naïve chronic hepatitis B patients: a case-control study. *Dig Dis Sci* 2014; 59(1): 168-173.
- Schweitzer A, Horn J, Mikolajczyk RT, Krause G, Ott JJ. Estimation of worldwide prevalence of chronic hepatitis B infection: a systematic review of data published between 1965 and 2013. *Lancet* 2015; 386(10003): 1546-55.
- Ali M, Idrees M, Ali L, Hussain A, ur Rehman I, Saleem S, et al. Hepatitis B virus in Pakistan: A systematic review of prevalence, risk factors, awareness status and genotypes. *Virology* 2011; 8: 102.
- Ono A, Suzuki F, Kawamura Y, Sezaki H, Hosaka T, Akuta N, et al. Long-term continuous entecavir therapy in nucleos(t)ide-naïve chronic hepatitis B patients. *J Hepatology* 2012; 57(3): 508-514.
- Chen GF, Wang C, Lau G. Treatment of chronic hepatitis B infection- 2017. *Liver Int* 2017; 37 (Suppl 1): 59-66.
- Bihl F, Alaei M, Negro F. The new EASL guidelines for the management of chronic hepatitis B infection adapted for Swiss physicians. *Swiss Med Wkly* 2010; 140(11-12): 154-159.
- Vallet-Pichard A, Pol S. Hepatitis B virus treatment beyond the guidelines: special populations and consideration of treatment withdrawal. *Therap Adv Gastroenterol* 2014; 7(4): 148-155.
- Dény P, Zoulim F. Hepatitis B virus: from diagnosis to treatment. *Pathol Biol (Paris)* 2010; 58(4): 245-253.
- Romero Díaz-Maroto V, Sánchez Cuervo M, Rodríguez Sagrado MÁ, Bermejo Vicedo T. Adherence to entecavir for chronic hepatitis B and correlation with effectiveness. *Farm Hosp* 2015; 39(6): 378-381.
- Sheppard-Law S, Zablotzka-Manos I, Kermeen M, Holdaway S, Lee A, George J. Factors associated with non-adherence to HBV antiviral therapy. *Antivir Ther* 2018; 23(5): 425-433.
- Tan X, Patel I, Chang J. Review of the four item morisky medication adherence scale (MMAS-4) and eight item morisky medication adherence scale (MMAS-8). *Inov Pharm* 2014; 5: 5.

## Hepatitis B Virus

14. Caviglia GP, Abate ML, Pellicano R, Smedile A. Chronic hepatitis B therapy: available drugs and treatment guidelines. *Minerva Gastroenterol Dietol* 2015; 61(2): 61-70.
  15. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. Geneva: WHO; 2015 [Internet]. Available at: <https://www.who.int/publications-detail-redirect/9789241549059> [Accessed on March 27, 2019].
  16. Allard N, Dev A, Dwyer J, Srivasta G, Thompson A, Cowie B. Factors associated with poor adherence to antiviral treatment for Hepatitis B. *J Viral Hepatol* 2017; 24(1): 53-8.
  17. Giang L, Selinger CP, Lee AU. Evaluation of adherence to oral antiviral hepatitis B treatment using structured questionnaires. *World J Hepatol* 2012; 4(2): 43-49.
  18. Chotiyaputta W, Hongthanakorn C, Oberhelman K, Fontana RJ, Licari T, Lok AS. Adherence to nucleos(t)ide analogues for chronic hepatitis B in clinical practice and correlation with virological breakthroughs. *J Viral Hepat* 2012; 19(3): 205-212.
  19. Xu K, Liu LM, Farazi PA, Wang H, Rochling FA, Watanabe-Galloway S. Adherence and perceived barriers to oral antiviral therapy for chronic hepatitis B. *Glob Health Action* 2018; 11: 1433987.
  20. Tordoff J, Simonsen K, Thomson WM, Norris PT. "It's just routine." A qualitative study of medicine-taking amongst older people in New Zealand. *Pharm World Sci* 2010; 32(2): 154-161.
  21. Ford N, Scourse R, Lemoine M, Hutin Y, Bulterys M, Shubber Z, et al. Adherence to nucleos(t)ide analogue therapies for chronic hepatitis B infection: a systematic review and meta-analysis. *Hepatol Commun* 2018; 2(10): 1160-1167.
  22. Kayaaslan B, Guner R. Adverse effects of oral antiviral therapy in chronic hepatitis B. *World J Hepatol* 2017; 9(5): 227-241.
  23. Lee M, Keeffe EB. Study of adherence comes to the treatment of chronic hepatitis B. *J Hepatol* 2011; 54(1): 6-8.
- .....