Adherence to Nucleos(t)ide Analogue Therapies for Chronic Hepatitis B Infection: A Systematic Review and Meta-Analysis

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Successful treatment outcomes for chronic hepatitis B virus (HBV) infection requires high levels of adherence to treatment. We searched three databases and abstracts from two conferences up to January 2018 for studies reporting the proportion of patients who were adherent to HBV antiviral therapy and pooled data using random effects meta-analysis. We included 30 studies, providing data for 23,823 patients. Overall, adherence to treatment was 74.6% (95% confidence interval [CI] 67.1%-82.1%). Adherence was similar in high-income settings (75.1%; 95% CI, 65.4%-85.0%) and in low-income and middle-income settings (72.9%; 95% CI, 57.8%-88.0%). Reported barriers to adherence included forgetting, limited understanding of the importance of adherence, and change to routine. *Conclusion*: There is a need to reinforce assessment and reporting of adherence as a routine part of HBV care and to assess the extent to which evidence-based interventions to improve adherence to medication for human immunodeficiency virus [HIV] and other chronic diseases are effective for HBV infection. (*Hepatology Communications* 2018;2:1160-1167).

According to World Health Organization estimates, 257 million persons were living with chronic HBV infection worldwide in 2015, with over two thirds (68%) of infections in the African and Western Pacific regions. Together, HBV and hepatitis C virus are responsible for 1.2 million deaths from cirrhosis and hepatocellular carcinoma each year, with two thirds of these deaths attributable to HBV.[1]

Antiviral therapy for HBV is effective in suppressing HBV viral load and reducing the risk of developing cirrhosis and hepatocellular carcinoma.[2,3] Treatment efficacy is dependent on high levels of adherence to medication; reduced adherence is the main driver of suboptimal treatment response[4] and can lead to viral failure, HBV flares, and increased morbidity and mortality.[5,6]

Ensuring high levels of adherence to chronic medication is a challenge[7,8]; however, the overall proportion of patients adherent to HBV medication and associated risk factors have not been assessed. We undertook a systematic review and meta-analysis to provide an overall estimate of adherence to nucleos(t)ide reverse transcriptase inhibitor-based therapy for chronic HBV infection and to identify reported barriers to adherence.

Abbreviations: CI, confidence interval; HBV, hepatitis B virus; HIV, human immunodeficiency virus.

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Materials and Methods

SEARCH STRATEGY AND SELECTION CRITERIA

This systematic review was conducted according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines[9] and followed a study protocol (available from the corresponding author).

Prospective and retrospective observational studies that provided quantitative data on adherence to HBV therapy for ≥10 patients were included for review. Because the aim of this review was to assess adherence in program settings, randomized controlled trials were excluded as adherence rates are likely to be higher in trials compared to routine treatment cohorts due to the patient selection prior to trial inclusion and support provided to study participants. There is no gold standard for measuring adherence to medication. We included studies that used both subjective measures (self-report) and objective measures (pill count, plasma drug levels, pharmacy claims, and electronic medical records). Viral load was not considered as this can be influenced by factors other than patient adherence. If studies reported outcomes among patients who had previously experienced treatment failure, these patients were excluded from analysis; if this was not possible, these studies were excluded from the review. Studies that used interferon-based regimens were also excluded from review due to the high adverse event rate associated with this drug likely leading to lower adherence. Finally, we excluded studies that included patients with hepatitis C and hepatitis D coinfection if data could not be disaggregated by coinfection status (because patients who are coinfected will likely have different adherence due to pill burden, disease status, and other challenges associated with comorbidities). No language, date, or geographic limitations were applied.

Using a sensitive search strategy that combined terms for hepatitis B infection, antiviral drugs, and adherence, two investigators (N.F., R.S.) screened titles and abstracts from MEDLINE through PubMed, Embase, and the Cochrane Library to January 31, 2018. Abstracts from conferences of the European Association for the Study of the Liver and American Association for the Study of Liver Diseases were screened from 2015 to 2017 to identify recent studies that may have been completed but not yet published in full. Database searches were supplemented by screening bibliographies of review articles and all included full-text articles. The same investigators scanned all abstracts and full-text articles and achieved consensus on final study inclusions. If multiple studies reported outcomes for the same cohort of patients, the study with the longest follow-up period was used as the primary study. If studies reported adherence at multiple time points, the longest time point was reported.

Three reviewers working independently (R.S., N.F., Z.S.) extracted data using a standardized and piloted extraction form that included study characteristics (design, year, population, location, HIV coinfection status, adherence measure); outcomes, including numbers adherent, and reasons for suboptimal adherence; and type of HBV therapy. Risk of bias was assessed using an adapted prevalence critical appraisal tool.[10]

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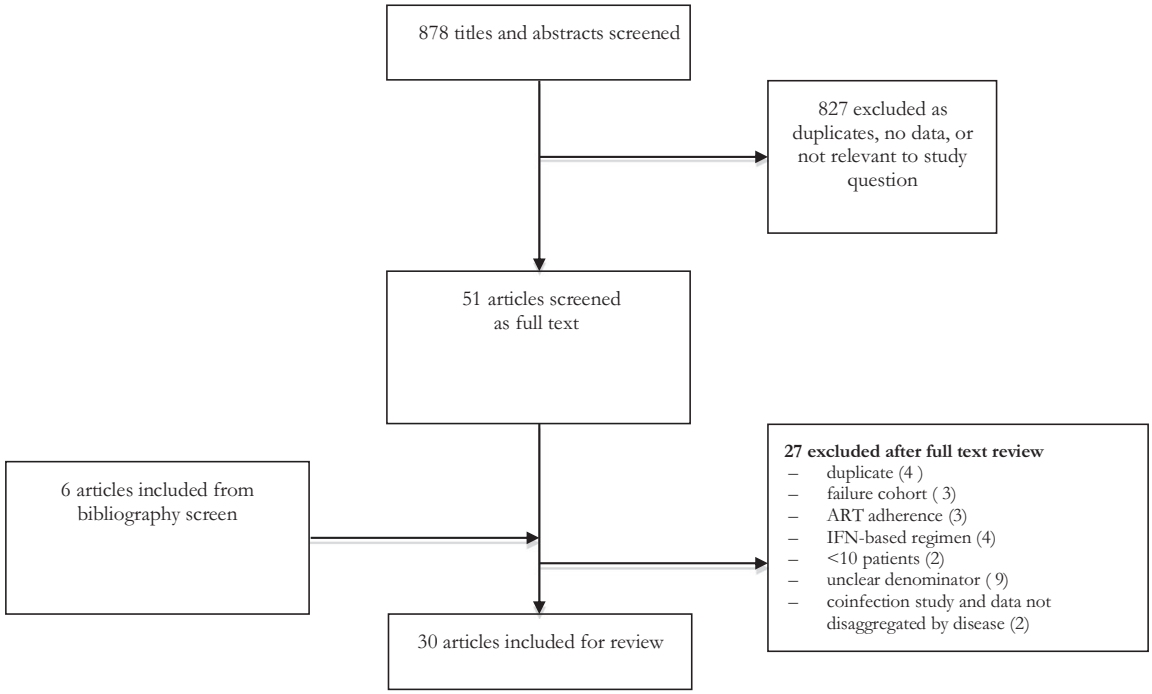

FIG. 1. Study selection process. Abbreviations: ART, antiretroviral therapy; IFN, interferon.

STATISTICAL ANALYSIS

Numerators and denominators for the number of patients considered optimally adherent within a given cohort were extracted according to adherence thresholds as defined by the studies (Supporting Table S1) and from these point estimates and corresponding 95% CIs were calculated and data were pooled following transformation using random-effects meta-analysis.[11,12] Results were stratified by country income status according to World Bank classification. The I^2 tests for heterogeneity is not a reliable test for pooled proportions,[13] and therefore for this review, heterogeneity was assessed using the τ^2 statistic (a measure of the variance of the effect size parameters across the population of studies) and through visual inspection of forest plots and subgroup analyses assessing the following covariates: income setting, adherence measure, and duration of follow-up. Meta-regressions were carried out to assess the potential influence of income setting, duration of follow-up, adherence measure, and proportion of male individuals. We analyzed all data with Stata version 13.0.

Results

From an initial screen of 878 titles, 30 studies providing data for 23,823 patients met our eligibility criteria and were taken through for review (Fig. 1).[4-6,14-39] The majority (23 studies, 17,057 patients) were from high-income settings, mainly the United States (seven studies), Australia (four studies), and France (three studies). Studies from low-income and middle-income settings were carried out in Brazil,[15,29] China,[31,33] The Gambia,[40] India,[24] and Zambia.[36] Twelve studies were prospective cohorts, 11 were retrospective cohorts, and seven were cross-sectional surveys. Most studies used self-report (11 studies) as the main adherence measure. All studies were carried out in adults, and in all studies the proportion of male patients was >50%. Most studies (14) gave patients a single-drug therapy, with the rest providing a combination of single or dual therapies; entecavir was the most common drug used (13 studies). Three studies included patients coinfected with HIV. Follow-up ranged from 4 months to 160 months, with a median follow-up of 16 months. Characteristics of included studies are provided in

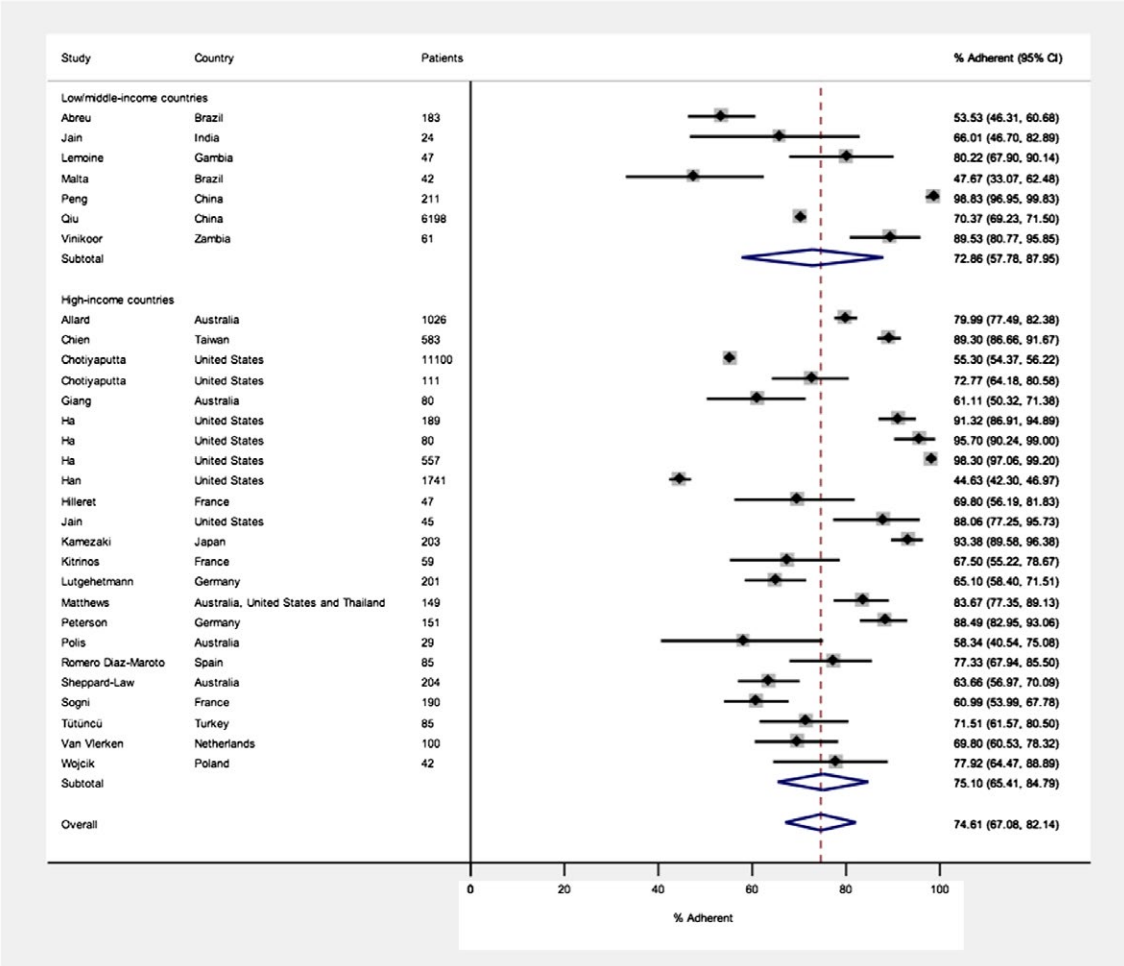

FIG. 2. Pooled proportion of patients adherent to HBV medication. Data points represent percentage adherence and 95% CI. Diamonds represent pooled proportions. Dotted line indicates the overall pooled proportion.

Supporting Table S1, and the risk of bias assessment is provided in Supporting Table S2.

Overall, adherence to treatment was 74.6% (95% CI, 67.1%-82.1%; $\tau^2 = 0.14$). Adherence was similar in high-income settings (75.1%; 95% CI, 65.4%-85.0%; $\tau^2 = 0.20$) and in low-income and middle-income settings (72.9%; 95% CI, 57.8%-88.0%; $\tau^2 = 0.21$). There was substantial heterogeneity (Fig. 2). Adherence stratified by adherence measure was as follows: plasma drug levels, 68.5% (95% CI, 59.9%-77.2%); medicine possession ratio, 69.1% (95% CI, 58.8%-79.4%); self-report, 69.5% (95% CI, 56.0%-82.9%); electronic medication dispenser, 69.8% (95% CI, 60.9%-78.7%); Morisky medication adherence scale, 87.0% (95% CI, 82.9%-91.1%); pharmacy claims, 88.1% (95% CI, 78.8%-97.3%); pill count, 73.1% (95% CI, 49.6%-96.5%); and electronic medical records, 95.4% (95% CI, 91.0%-99.8%). In subgroup analysis, there was no difference in adherence when studies with a follow-up duration greater than 12 months (77.4%; 95% CI, 67.7%-87.0%) were compared to those with 12 months or less (81.0%; 95% CI, 63.8%-98.2%), or comparing studies that used self-report as an adherence measure (70.2%; 95% CI, 57.6%-82.9%) versus objective measures (77.1%; 95% CI, 67.4%-86.8%), or studies that defined optimal adherence as 100% adherence (75.0%; 95% CI, 67.5%-82.5%) versus <100% adherence (70.6%; 95% CI, 63.3%-77.9%). These findings were consistent with the results of the meta-regression, which was unable to identify an association between these covariates and adherence outcomes (Supporting Table S3). We also used meta-regression to explore a possible association

between the proportion of male participants (which ranged from 55%-100%) and adherence, but again found no association.

Barriers to adherence were reported by seven studies.[5,20,21,24,28,32,39] Among patients with suboptimal adherence, 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%). Other challenges, reported by single studies included travel (13.3%; 95% CI, 3.8%-30.7%), cost of care (70.0%; 95% CI, 45.7%-88.1%), being busy (12.9%; 95% CI, 3.6%-29.8%), "ran out of drugs" (16.1%; 95% CI, 5.4%-33.7%), and no perceived improvement in health status (50%; 95% CI, 27.2%-72.8%).

Discussion

Achieving high levels of adherence is key to successful treatment outcomes for chronic HBV infection. Modeling studies suggesting that, compared to optimal adherence of 95%, a lower adherence of 65% would lead to 2.6 million additional deaths over a 15-year period.[41] Our systematic review found moderate adherence to treatment for chronic HBV infection. Overall, three in four patients were reported to be adherent to chronic HBV infection medication, and while the optimal level of adherence required to achieve therapeutic efficacy is not established and may vary by regimen, this is higher than reported for HIV infection.[7] In this review, the most common measure of adherence was self-report, and although we found no major difference in adherence by measure, other studies have found that self-report overestimates adherence,[42] a finding consistent with other disease areas.[43] If confirmed, the overall pooled estimate for adherence is likely to be lower than reported by this review.

This review aimed to estimate the proportion of patients who are adherent to chronic HBV infection medication. There is no gold standard for measuring adherence, and while viral load is considered to be the preferred measure, viral load can be influenced by factors other than adherence, including drug efficacy, polypharmacy, drug resistance, treatment failure, and unknown effects of the disease or drugs. For this reason, we did not include studies that reported viral load as the only adherence measure, and it would be valuable to summarize estimates of viral suppression separately to estimates of adherence, as has been done for HIV.[7,44,45] We also did not look at biochemical response (as defined by normalization of liver aminotransferase levels), which is influenced by other infectious diseases and chronic liver disease (especially nonalcoholic fatty liver disease in high-income countries).

Entecavir was the most widely used drug reported by studies in this review. Entecavir and tenofovir are both potent and safe drugs that can be used widely for HBV treatment with minimal laboratory monitoring and are the preferred options recommended by the World Health Organization. Entecavir also appears to have a high genetic barrier to resistance, although availability is limited in many settings because of its comparatively higher cost.

The only previous systematic review, published in 2012, included only six studies on chronic HBV infection treatment adherence.[46] That review did not provide a statistical summary of adherence estimates given the limited number of studies identified and concluded that nonadherence was infrequent. Our review suggests that suboptimal adherence is an important concern deserving attention. Few studies reported reasons for suboptimal adherence, but the limited information available is consistent with what is known for adherence to HIV medication, where the most commonly reported barriers to adherence include forgetting, change to routine, secrecy/stigma, distance to clinic, being busy, and stock outs.[45] This suggests that interventions to improve adherence to medication for HIV and other chronic infectious diseases may work for chronic HBV infection. Findings from a recent study suggest that text messaging could improve adherence to chronic HBV infection[47]; this is consistent with the larger body of evidence supporting text messaging to improve adherence to antiretrovirals for HIV.[48] Another promising approach to improve retention in care is to reduce the frequency of dispensing and clinic visits[49]; this approach is now widely recommended for HIV treatment and care.[50,51] Other proven strategies for improving adherence to HIV treatment that could be considered for chronic HBV infection include peer support and cognitive behavioral therapy.[48]

Strengths of this review include a broad search strategy that allowed for the identification of 24 additional articles compared to the previously published review.

We chose to exclude studies of patients with a history of treatment failure as it can be expected that such patients are more likely to be at risk of suboptimal adherence; however, routine clinic cohorts can be expected to include a proportion of such patients, and this may lead to lower overall adherence levels. In the final study selection process, only one study was excluded for this reason. We anticipated substantial heterogeneity in adherence reported from program settings and explored potential drivers of heterogeneity in several preplanned subgroup analyses. While these analyses were unable to identify patient or study characteristics that could explain variation in adherence (likely due to the small number of studies and inconsistent reporting of covariates), outlier analysis provided some further insights. Studies reporting lower average adherence included a study of noninjecting drug users in Brazil[29] and the use of older drugs associated with a greater frequency of adverse events. Other covariates that could explain potential differences in adherence, including age, disease progression and duration, and concomitant medication, were too infrequently reported to be able to assess. The main concerns with respect to risk of bias include retrospective study designs and the use of subjective adherence measures as well as different thresholds for defining optimal adherence, which ranged from >70% to 100% adherence (Supporting Table S1). The main limitation of this systematic review is the limited evidence base, in particular the limited reporting from low-income and middle-income settings; this partly reflects the fact that access to HBV therapy has until recently been limited in resource-limited settings, in particular Africa. As access to affordable treatment for HBV therapy is increasing globally, objective measures of adherence should be integrated into routine care. Publication bias is a concern for any systematic review and in particular for reviews of routine program performance (as only a minority of outcomes from routine programs are published). We cannot know how publication bias may affect the findings presented in this review as studies reported a range of adherence levels, indicating that publications are not limited to positive adherence results.

This review also found only limited information regarding patient-reported barriers to adherence, and there is a need for a better understanding of causes of nonadherence. More fundamentally, there is a need to improve awareness of the disease; in many low-income settings, knowledge of HBV in the general population is very limited, with less than 1% of people in The Gambia reporting to have heard of hepatitis B, although most are familiar with HIV and malaria.[52] Future research should focus both on identification of potential risk factors (including age, sex, coinfection status, and stage of disease) and patient-reported barriers to help identify patients at higher risk of nonadherence and supportive interventions. Consistent reporting of adherence measures would also help comparability of adherence estimates.

In conclusion, our review provides evidence of moderate levels of adherence to chronic hepatitis B medication but highlights that more attention is needed to further improve adherence. Further research is encouraged, particularly from low-income and middle-income settings, to better understand the causes of suboptimal adherence and to assess the impact of adherence-support interventions. Lessons can be learned from other chronic infectious disease areas, notably HIV.

REFERENCES

1) World Health Organization. Global Hepatitis Report. Geneva, Switzerland: World Health Organization; 2017.
2) Su TH, Hu TH, Chen CY, Huang YH, Chuang WL, Lin CC, et al. C-TEAM study group and the Taiwan Liver Diseases Consortium. Four-year entecavir therapy reduces hepatocellular carcinoma, cirrhotic events and mortality in chronic hepatitis B patients. Liver Int 2016;36:1755-1764.
3) Papatheodoridis GV, Idilman R, Dalekos GN, Buti M, Chi H, van Boemmel F, et al. The risk of hepatocellular carcinoma decreases after the first 5 years of entecavir or tenofovir in Caucasians with chronic hepatitis B. Hepatology 2017;66:1444-1453.
4) Ha NB, Trinh HN, Rosenblatt L, Nghiem D, Nguyen MH. Treatment outcomes with first-line therapies with entecavir and tenofovir in treatment-naive chronic hepatitis B patients in a routine clinical practice. J Clin Gastroenterol 2016;50:169-174.
5) 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;19:205-212.
6) Sogni P, Carrieri MP, Fontaine H, Mallet V, Vallet-Pichard A, Trabut JB, et al. The role of adherence in virological suppression in patients receiving anti-HBV analogues. Antivir Ther 2012;17:395-400.
7) Mills EJ, Nachega JB, Buchan I, Orbinski J, Attaran A, Singh S, et al. Adherence to antiretroviral therapy in sub-Saharan Africa and North America: a meta-analysis. JAMA 2006;296:679-690.
8) Chowdhury R, Khan H, Heydon E, Shroufi A, Fahimi S, Moore C, et al. Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences. Eur Heart J 2013;34:2940-2948.
9) Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.
10) Munn Z, Moola S, Lisy K, Riitano D, Tufanaru C. Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data. Int J Evid Based Healthc 2015;13:147-153.

11) Fleiss JL. The statistical basis of meta-analysis. Stat Methods Med Res 1993;2:121-145.
12) Freeman MF, Tukey JW. Transformations related to the angular and the square root. Ann Math Stat 1950;21:607-611.
13) Rucker G, Schwarzer G, Carpenter JR, Schumacher M. Undue reliance on I(2) in assessing heterogeneity may mislead. BMC Med Res Methodol 2008;8:79.
14) Petersen J, Wilke T, Mauss S, Heyne R, Herold C, Wiese M, et al. Persistence to entecavir treatment for chronic hepatitis B in a real-life setting: 2 year results of a German prospective multicentre observational study. [Abstract]. EASL LiverTree 2016. Abstract FRI-126.
15) Abreu RM, da Silva Ferreira C, Ferreira AS, Remor E, Nasser PD, Carrilho FJ, et al. Assessment of adherence to prescribed therapy in patients with chronic hepatitis B. Infect Dis Ther 2016;5:53-64.
16) Allard N, Dev A, Dwyer J, Srivatsa G, Thompson A, Cowie B. Factors associated with poor adherence to antiviral treatment for hepatitis B. J Viral Hepat 2017;24:53-58.
17) Chien RN, Peng CY, Kao JH, Hu TH, Lin CC, Hu CT, et al. Taiwan NA-Registry Group. Higher adherence with 3-year entecavir treatment than lamivudine or telbivudine in treatment-naive Taiwanese patients with chronic hepatitis B. J Gastroenterol Hepatol 2014;29:185-192.
18) 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.
19) Romero Diaz-Maroto V, Sanchez Cuervo M, Rodriguez Sagrado MA, Bermejo Vicedo T. Adherence to entecavir for chronic hepatitis B and correlation with effectiveness. Farm Hosp 2015;39:378-381.
20) Giang L, Selinger CP, Lee AU. Evaluation of adherence to oral antiviral hepatitis B treatment using structured questionnaires. World J Hepatol 2012;4:43-49.
21) Ha NB, Ha NB, Garcia RT, Trinh HN, Chaung KT, Nguyen HA, et al. Medication nonadherence with long-term management of patients with hepatitis B e antigen-negative chronic hepatitis B. Dig Dis Sci 2011;56:2423-2431.
22) 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-naive chronic hepatitis B patients: a case-control study. Dig Dis Sci 2014;59:168-173.
23) Hilleret MN, Larrat S, Stanke-Labesque F, Leroy V. Does adherence to hepatitis B antiviral treatment correlate with virological response and risk of breakthrough? J Hepatol 2011;55:1468-1469; author reply 1469-1470.
24) Jain M, Adkar S, Waghmare C. Adherence to oral antivirals in patients with chronic hepatitis B infection. Indian J Gastroenterol 2014;33:390-391.
25) Jain MK, Comanor L, White C, Kipnis P, Elkin C, Leung K, et al. Treatment of hepatitis B with lamivudine and tenofovir in HIV/HBV-coinfected patients: factors associated with response. J Viral Hepat 2007;14:176-182.
26) Kamezaki H, Kanda T, Arai M, Wu S, Nakamoto S, Chiba T, et al. Adherence to medication is a more important contributor to viral breakthrough in chronic hepatitis B patients treated with entecavir than in those with lamivudine. Int J Med Sci 2013;10:567-574.
27) Kitrinos KM, Corsa A, Liu Y, Flaherty J, Snow-Lampart A, Marcellin P, et al. No detectable resistance to tenofovir disoproxil fumarate after 6 years of therapy in patients with chronic hepatitis B. Hepatology 2014;59:434-442.
28) Lutgehetmann M, Meyer F, Volz T, Lohse AW, Fischer C, Dandri M, et al. Knowledge about HBV, prevention behaviour and treatment adherence of patients with chronic hepatitis B in a large referral centre in Germany. Z Gastroenterol 2010;48:1126-1132.
29) Malta M, Cavalcanti S, Gliksman L, Adlaf E, Hacker Mde A, Bertoni N, et al. Behavior and major barriers faced by non-injectable drug users with HBV/HCV seeking treatment for hepatitis and drug addiction in Rio de Janeiro. Brazil. Cien Saude Colet 2011;16:4777-4786.
30) Matthews GV, Seaberg EC, Avihingsanon A, Bowden S, Dore GJ, Lewin SR, et al. Patterns and causes of suboptimal response to tenofovir-based therapy in individuals coinfected with HIV and hepatitis B virus. Clin Infect Dis 2013;56:e87-e94.
31) Peng J, Yin J, Cai S, Yu T, Zhong C. Factors associated with adherence to nucleos(t)ide analogs in chronic hepatitis B patients: results from a 1-year follow-up study. Patient Prefer Adherence 2015;9:41-45.
32) Polis S, Zablotska-Manos I, Zekry A, Maher L. Adherence to hepatitis B antiviral therapy: a qualitative study. Gastroenterol Nurs 2017;40:239-46.
33) Qiu Q, Duan XW, Li Y, Yang LK, Chen Y, Li H, et al. Impact of partial reimbursement on hepatitis B antiviral utilization and adherence. World J Gastroenterol 2015;21:9588-9597.
34) Sheppard-Law S, Zablotska-Manos I, Kermeen M, Holdaway S, Lee A, Zekry A, et al. Factors associated with HBV virological breakthrough. Antivir Ther 2017;22:53-60.
35) van Vlerken LG, Arends P, Lieveld FI, Arends JE, Brouwer WP, Siersema PD, et al. Real life adherence of chronic hepatitis B patients to entecavir treatment. Dig Liver Dis 2015;47:577-583.
36) Vinikoor MJ, Sinkala E, Chilengi R, Mulenga LB, Chi BH, Zyambo Z, Africa IeDEA- Southern, et al. Impact of antiretroviral therapy on liver fibrosis among human immunodeficiency virus-infected adults with and without HBV coinfection in Zambia. Clin Infect Dis 2017;64:1343-1349.
37) Wojcik K, Piekarska A, Jablonowska E. Adherence to antiviral therapy in HIV or HBV-infected patients. Przegl Epidemiol 2016;70:27-32, 115-118.
38) Han SH, Jing W, Mena E, Li M, Pinsky B, Tang H, et al. Adherence, persistence, healthcare utilization, and cost benefits of guideline-recommended hepatitis B pharmacotherapy. J Med Econ 2012;15:1159-1166.
39) Tutuncu EE, Guner R, Gurbuz Y, Kaya Kalem A, Öztürk B, Hasanoğlu İ, et al. Adherence to nucleoside/nucleotide analogue treatment in patients with chronic hepatitis B. Balkan Med J 2017;34:540-545.
40) Lemoine M, Shimakawa Y, Njie R, Taal M, Ndow G, Chemin I, et al. PROLIFICA investigators. Acceptability and feasibility of a screen-and-treat programme for hepatitis B virus infection in The Gambia: the Prevention of Liver Fibrosis and Cancer in Africa (PROLIFICA) study. Lancet Glob. Health 2016;4:e559-e567.
41) Nayagam S, Thursz M, Sicuri E, Conteh L, Wiktor S, Low-Beer D, et al. Requirements for global elimination of hepatitis B: a modelling study. Lancet Infect Dis 2016;16:1399-1408.
42) Chotiyaputta W, Oberhelman K, Hongthanakorn C, Conjeevaram Hari S, Fontana Robert J, Licari Tracy, et al. Correlation between self-reported adherence to nucleos(t)ide analog (NUC) therapy for chronic hepatitis B (CHB) and virological breakthroughs (VBT). AASLD. Hepatology 2010;52:542A.
43) Sangeda RZ, Mosha F, Prosperi M, Aboud S, Vercauteren J, Camacho RJ, et al. Pharmacy refill adherence outperforms self-reported methods in predicting HIV therapy outcome in resource-limited settings. BMC Public Health 2014;14:1035.
44) Boender TS, Sigaloff KC, McMahon JH, Kiertiburanakul S, Jordan MR, Barcarolo J, et al. Long-term virological outcomes of first-line antiretroviral therapy for HIV-1 in low- and middle-income countries: a systematic review and meta-analysis. Clin Infect Dis 2015;61:1453-1461.

45) Shubber Z, Mills EJ, Nachega JB, Vreeman R, Freitas M, Bock P, et al. Patient-reported barriers to adherence to antiretroviral therapy: a systematic review and meta-analysis. PLoS Med 2016;13:e1002183.
46) Lieveld FI, van Vlerken LG, Siersema PD, van Erpecum KJ. Patient adherence to antiviral treatment for chronic hepatitis B and C: a systematic review. Ann Hepatol 2013;12:380-391.
47) Abreu RM, Hori PCA, Rocha P, Minari AB, Dias MA, Pinto VB, et al. Text message reminders increase antiviral therapy adherence in chronic hepatitis B patients [Abstract]. Eur J Hosp Pharm 2016;23(Suppl. 1):A49-A50.
48) Kanters S, Park JJ, Chan K, Socias ME, Ford N, Forrest JI, et al. Interventions to improve adherence to antiretroviral therapy: a systematic review and network meta-analysis. Lancet HIV 2017;4:e31-e40.
49) Ruiz Gómez MA, Martínez Nieto C, Ramírez Herraiz E, Diaz Gomez E, Perez Abanades M, Serra Lopez-Matencio JM, et al. Impact on drug adherence and viral load after pharmaceutical intervention in selected hepatitis B outpatients. Eur J Hosp Pharm 2016;23(Suppl. 1):A65.
50) Mutasa-Apollo T, Ford N, Wiens M, Socias ME, Negussie E, Wu P, et al. Effect of frequency of clinic visits and medication pick-up on antiretroviral treatment outcomes: a systematic literature review and meta-analysis. J Int AIDS Soc 2017;20(Suppl. 4):21647.
51) World Health Organization. Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a Public Health Approach, 2nd edn. Geneva, Switzerland: World Health Organization; 2016.
52) Shimakawa Y, Pourette D, Bainilago L, Enel C, Sombié R, Rado R, et al. Improving communication about viral hepatitis in Africa. Lancet Infect Dis 2017;17:688-689.

Supporting Information

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