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REVIEW

Adverse events of nucleos(t)ide analogues for chronic hepatitis B: a systematic review

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Abstract Nucleos(t)ide analogues (NAs) are the main drug category used in chronic hepatitis B (CHB) treatment. Despite the fact that NAs have a favourable safety profile, undesired adverse events (AEs) may occur during the treatment of CHB. Given the eminent number of patients currently receiving NAs, even a small risk of any of these toxicities can represent a major medical issue. The main objective of this review was to analyse information available on AEs associated with the use of NAs in published studies. We choose the following MesH terms for this systematic review: chronic hepatitis B, side effects and treatment. All articles published from 1 January 1990 up to 19 February 2018 in MEDLINE of PubMed, EMBASE, the Cochrane Library and LILACS databases were searched. A total of 120 articles were selected for analysis, comprising 6419 patients treated with lamivudine (LAM), 5947 with entecavir (ETV), 3566 with tenofovir disoproxil fumarate (TDF), 3096 with telbivudine (LdT), 1178 with adefovir dipivoxil (ADV) and 876 with tenofovir alafenamide (TAF). The most common AEs in all NAs assessed were abdominal pain/discomfort, nasopharyngitis/upper respiratory tract infections, fatigue, and headache. TAF displays the highest density of AEs per patient treated among NAs (1.14 AE/treated patient). In conclusion, treatment of CHB with NAs is safe, with a low incidence of AEs. Despite the general understanding TAF being safer than TDF, the number of patients treated with TAF still is too small in comparison to other NAs to consolidate an accurate safety profile. PROSPERO Registration No. CRD42018086471

Keywords Chronic hepatitis B · Nucleotide/nucleoside analogues · Adverse events

Introduction

An estimated 257 million people globally are living with chronic hepatitis B (CHB) infection, according to the World Health Organization in 2018 [1]. Treatment's main goals in CHB are to halt disease progression and prevent disease-related complications, achieved by suppression of hepatitis B virus (HBV) DNA replication [2]. To the present date, CHB treatment is either based on nucleos(t)ide analogue (NA) or on interferon IFNα, currently pegylated (PegIFNα) [3, 4]. NAs that have been approved for HBV treatment in humans include lamivudine (LAM), adefovir dipivoxil (ADV), entecavir (ETV), telbivudine (LdT), tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF), and can be classified into those associated with low barrier against HBV resistance (LAM, ADV, LdT) and those with high barrier to HBV resistance (ETV, TDF, TAF) [3–5]. The main advantage of treatment with a potent NA with high barrier to resistance (i.e., ETV, TDF, TAF), considered to be the first-line treatment for CHB, is its predictable high long-term antiviral efficacy leading to undetectable HBV DNA levels in the vast majority of compliant patients as well as its good safety profile [3–5]. Moreover, it has been shown that NAs can improve the

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liver fibrosis and reduce the hepatocarcinogenesis in patients with CHB [6–8].

A significant number of patients has been treated with NAs to date, having increased the experience with their efficacy, resistance and safety profile over the years. Despite the fact that NAs have a favourable safety profile [3, 4], undesired adverse events (AEs) may occur during the treatment of CHB infection. Given the eminent number of patients currently receiving NAs, even a small risk of any of these toxicities can be translated into a major medical issue.

The main objective of this systematic review is to analyse available information in published studies on AEs associated with Nas' use in adults.

Methods

Eligibility criteria

The following research questions were addressed:

- What are the most common AEs with the use of NAs in the CHB treatment?
- Is there any difference in the incidence of AEs between the different NAs?
- Do patients receiving TAF have fewer AEs compared to TDF?

A PICO model was constructed (participants, interventions, control and outcome):

Participants

- Adults > 18 years old diagnosed with HBV infection.

Interventions

- Antiviral therapy with NAs (LAM, ADV, LdT, ETV, TDF or TAF).

Control

- We used only the data for the currently approved dose, i.e. LAM 100 or 150 mg; ADV 10 mg; LdT 600 mg; ETV 0,5 or 1,0 mg; TDF 300 mg; TAF 25 mg.
- Studies based only on drug-combination regimens were excluded due to difficulties in evaluating cause–effect relationship.
- Studies with both single drug arm and drug-combinations arm; only the single drug arm were included in the analysis.

Outcome measure

- Adverse events (AEs).

Exclusion criteria

We excluded studies whose patients presented acute HBV infection, acute liver failure, decompensated cirrhosis, pregnancy, hepatitis C or D or human immunodeficiency virus (HIV) coinfection, schistosomiasis infection; patients receiving corticosteroids, chemotherapy, or immunosuppressive therapy; transplant recipients; and hemodialysis patients. Likewise, studies that did not report AEs or stated "no serious adverse events" or "no significant difference in side effects between groups" with no further AEs description were excluded.

Literature search strategy

This study was performed according to the PRISMA statement [9]. We chose the following MesH terms: chronic hepatitis B, side effects and treatment. We reviewed all articles published from 1 January 1990 up to 19 February 2018 in MEDLINE of PubMed, EMBASE, the Cochrane Library and LILACS databases and included studies published in English language. Since the NAs have a good safety profile with a small percentage of AEs, we enrolled both observational (i.e. cohort, case–control and cases series) and randomized controlled trials (RCTs) as a search strategy for maximizing AEs sensitivity. All the references identified were managed by Endnote. The flowchart in Fig. 1 shows the process of review of publications. We followed an established protocol which had been registered in PROSPERO (International prospective register of systematic reviews) [10], and the record is available on https://www.crd.york.ac.uk/prospero/ (Registration No. CRD42018086471).

Data collection and quality assessment

The following data were extracted from included studies: study design, country where the study was conducted, first author, publication year, number of participants, inclusion and exclusion criteria, drug dosing regimens and AEs reported. Two reviewers independently performed data extraction (RSF and VVV) and discrepancies were discussed during a consensus meeting.

To facilitate data analysis, AEs were divided into groups, similar to those found in the VigiAccess™ database, as follows: blood and lymphatic system disorders; cardiac disorders; ear and labyrinth disorders; endocrine disorders; eye disorders; gastrointestinal disorders; general

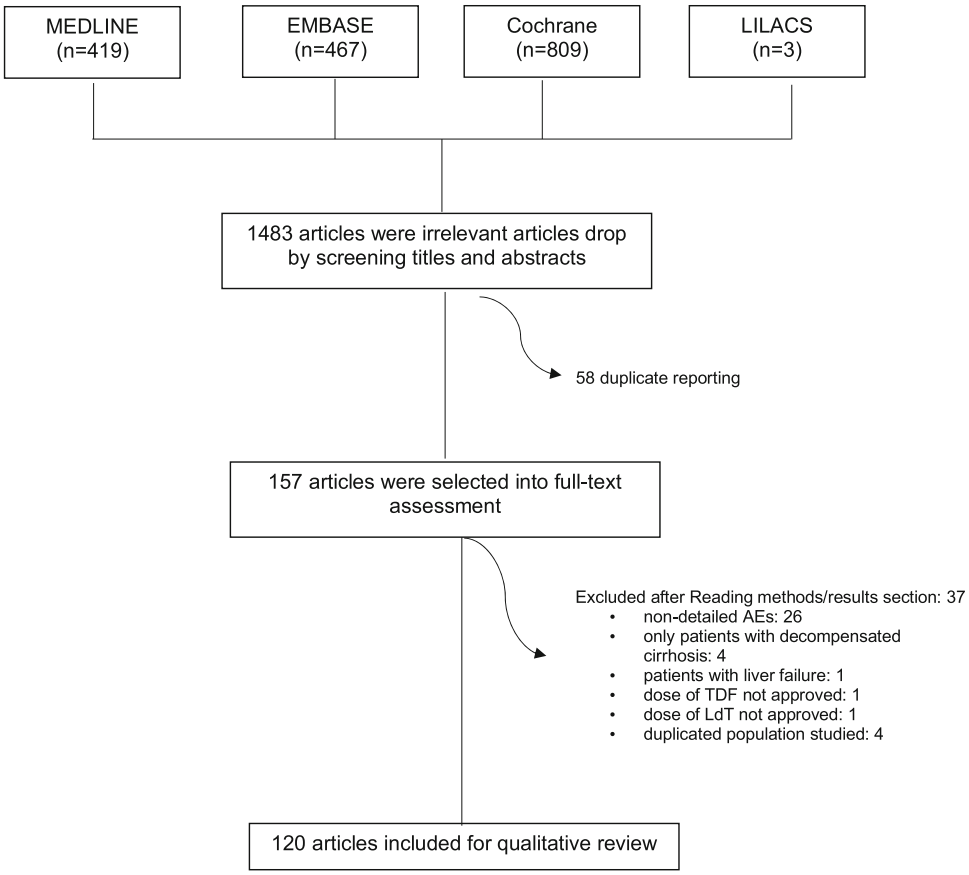

Figure1 Flowchart of study selection. *MEDLINE* Medical Literature Analysis and Retrieval System Online, *EMBASE* Excerpta Medica Database, *Cochrane* The Cochrane Library, *LILACS* Literatura Latino–Americana e do Caribe em Ciências da Saúde, *AEs* adverse events, *TDF* tenofovir disoproxil fumarate, *LdT* telbivudine

disorders; hepatobiliary disorders; infections and infestations; laboratory abnormalities; metabolism and nutrition disorders; musculoskeletal and connective tissue disorders; neoplasms; nervous system disorders; psychiatric disorders; renal and urinary disorders, reproductive system disorders; respiratory disorders; skin and subcutaneous tissue disorders.

Results

Studies

A total of 1698 articles were retrieved. Two authors conducted an initial screening and 1483 studies were excluded after reading titles and abstracts. Following the removal of duplicates, 157 full-text articles were assessed for eligibility. Thirty-seven studies were excluded for the following reasons: non-detailed adverse events (26), only patients with decompensated cirrhosis (4), patients with liver failure (1), dose of TDF not approved (1), dose of LdT not approved (1) and duplicated population studied (4). Finally, 120 articles were selected for analysis. The listing of the included reporters and their characteristics are shown in Table 1.

There were 6419 patients treated with LAM, 5947 treated with ETV, 3566 treated with TDF, 3096 treated with LdT, 1178 treated with ADV and 876 treated with TAF.

Table 2 contains the AEs described in the studies, depending on the drugs used.

Neoplasms were documented in 39 patients, with hepatocellular carcinoma being the most frequent– 67% (*n*. 26: LAM-8; ETV-9; TDF-3; LdT-6) [Table 2]. None of the cases were related to NAs use.

Lamivudine (LAM)

In studies using 100 mg of LAM, a total of 5554 AEs were reported (0.87 AE/patient treated) [Fig. 2, Table 2].

The most frequent AEs reported were gastrointestinal disorders (20.1%), infections and infestations (15.7%), general disorders (14.6%), respiratory disorders (12.5%) and nervous system disorders (12%) [Table 2].

Among gastrointestinal events, the most reported were abdominal pain or discomfort (n = 411).

The most commonly described infections were upper respiratory tract infection (n = 413).

General disorders included nonspecific symptoms, with asthenia/fatigue being the most reported (n = 672).

Table 1 Studies reported in this review

Authors, year	Country	Patients (*n*)	Drugs	Study design
Koike, 2018 [39]	Japan	110	TDF	Randomized, active controlled, double-blind, double-dummy, parallel arm comparation
		56	ETV	
An, 2017 [40]	Republic of Korea	47	ETV	Randomized open-label
		50	LdT	
Ashgar, 2017 [41]	Saudi Arabia	23	PEGIFN ∝ -2a + TDF	Randomized controlled
		25	TDF	
Du Jeong, 2017 [42]	Republic of Korea	391	TDF	Retrospective observational
Fung, 2017 [43]	Multiple countries	141	TDF	Prospective, randomized, double-blind, double-dummy
		139	FTC/TDF	
Lee, 2017 [44]	Republic of Korea	56	ETV	Phase 4, randomized
		64	LAM	
Luo, 2017 [45]	China	91	LdT	Prospective "real-life"
		93	ETV	
Rodríguez, 2017 [46]	Spain	22	TDF	Phase 4, prospective, randomized, open, controlled
		24	LAM + ADV	
Yang, 2017 [47]	China	107	LAM + vaccine	Double-blind, randomized, placebo-controlled
		115	LAM + placebo	
Wu, 2017 [48]	Taiwan	106	TDF	Retrospective observational
		313	ETV	
Ahn, 2016 [49]	USA	658	ETV	Observational, retrospective cohort ("real world")
Buti, 2016 [29]	Multiple countries	285	TAF	Randomized, double-blind, phase 3, non-inferiority
		140	TDF	
Chan, 2016 [30]	Multiple countries	581	TAF	Randomized, double-blind, non-inferiority
		292	TDF	
Huang, 2016 [50]	China	79	TDF	Retrospective cohort
		45	TDF + NAs	
Lim, 2016 [51]	Republic of Korea	45	TDF	Randomized open-label
		45	TDF + ETV	
Marcellin, 2016 [52]	France	440	TDF	Non-interventional, prospective
Marcellin, 2016 [53]	Multiple countries	185	PEGIFN ∝ -2a	Randomized open-label, controlled
		185	TDF	
		186	PEGIFN ∝ -2a + TDF	
		184	PEGIFN ∝ -2a + TDF16 w + TDF alone 32 w	
Shen, 2016 [54]	China	65	LdT	Prospective randomized
		65	ETV	
Zhang, 2016 [55]	China	99	ETV	Prospective cohort
		97	LdT	
Agarwal, 2015 [56]	UK	10	TAF 8 mg	Randomized open-label, phase 1b
		10	TAF 25 mg	
		11	TAF 40 mg	
		10	TAF 120 mg	
		10	TDF	

Table 1 continued

Authors, year	Country	Patients (*n*)	Drugs	Study design
Alsohaibani, 2015 [57]	Saudi Arabia	68	TDF	Retrospective, observational
Hou, 2015 [58]	China	257	TDF	Randomized controlled
		252	ADV	
Hou, 2015 [59]	China	57	LdT	Cohort
Huang, 2015 [60]	China	33	TDF	Retrospective, observational
		65	ETV	
Jia, 2015 [61]	China	68	ADV + LAM	Case–control (prospective)
		68	ETV	
Kim, 2015 [62]	Republic of Korea	52	TDF	Retrospective observational
Kim, 2015 [63]	Republic of Korea	61	LdT	Retrospective observational
		90	ETV	
Kwon, 2015 [64]	Republic of Korea	39	TDF	Retrospective observational
		42	ETV	
Marcellin, 2015 [65]	Multiple countries	50	PEGIFN ∝ -2a + LdT	Randomized,open-label
		54	PEGIFN ∝ -2a	
		55	LdT	
Yuen, 2015 [66]	Republic of Korea	31	Besifovir 90 mg	Randomized open-label, phase 2b
		28	Besifovir 150 mg	
		30	ETV	
Ahn, 2014 [67]	Republic of Korea	411	TDF	Retrospective, observational
Berg, 2014 [68]	France, Germany, USA	53	TDF	Randomized, double-blind
		52	TDF/FTC	
Chan, 2014 [69]	Multiple countries	62	TDF/FTC	Randomized, double-blind, phase 2
		64	TDF	
Fung, 2014 [70]	Multiple countries	141	TDF	Randomized, double-blind
		130	TDF/FTC	
Jia, 2014 [71]	China	167	LdT	Randomized, phase 3
		165	LAM	
Lai, 2014 [72]	Hong Kong		Besifovir 90 mg	Randomized open-label, phase 2b
			Besifovir 150 mg	
			ETV	
Leung,2014 [73]	China	16	LdT	Randomized, open-label
	Germany	14	TDF	
	Switzerland	16	LdT + TDF	
Ozaras, 2014 [74]	Turkey	121	TDF	Cohort
		130	ETV	
Pan, 2014 [75]	USA	90	TDF	Open-label, single-arm, phase 4
Sun, 2014 [76]	China	300	LdT + ADV	Randomized, open-label, controlled
		299	LdT	
Du, 2013 [77]	China	25	LAM + ADV	Prospective, randomized (pilot study)
		25	ETV	
Gwak, 2013 [78]	Republic of Korea	50	Clevudine	Comparative retrospective
		58	ETV	
Hou, 2013 [79]	China	2600 (54 patients excluded of analysis – decompensated cirrhosis)	ETV	Prospective, observational cohort

Table 1 continued

Authors, year	Country	Patients (*n*)	Drugs	Study design
Li, 2013 [80]	China	14	LAM (test)	Randomized, open-label
		14	LAM (branded reference)	
Li,2013 [81]	China	42	LdT	Open-label, single-arm
Lian, 2013 [82]	China	60	ADV + LAM	Prospective case–control
		60	ETV	
Lu, 2013 [83]	China	30	LdT + ADV	Randomized open-label
		28	ETV	
Luo, 2013 [84]	China	230	ETV	Retrospective observational
Marcellin, 2013 [85]	Multiple countries	389	TDF	Randomized, open-label
		196	ADV followed TDF	
Wang, 2013 [86]	China	30	LAM + ADV	Randomized open-label
		25	ETV	
Butti, 2012 [87]	Spain	190	ETV	Retrospective, observational
Heo, 2012 [88]	Republic of Korea	36	ETV	Randomized open-label phase 4
		36	LAM	
Lok, 2012 [89]	Multiple countries	198	ETV + TDF	Randomized open-label phase 3b
		186	ETV	
Gane, 2011 [90]	Multiple countries	389	LdT	Open-label, single-arm
Patterson, 2011 [91]	Australia	38	TDF	Prospective open-label
		22	TDF + LAM	
Perrillo, 2011 [92]	Multiple countries	48	LAM + placebo	Randomized open-label
		94	LAM + ADV	
Safadi, 2011 [93]	Multiple countries	122	LdT	Randomized, double-blind, phase 3b
		124	LAM	
Shin, 2011 [94]	Republic of Korea	109	clevudine	Comparative retrospective
		283	ETV	
Wang, 2011 [95]	China	28	LAM	Prospective controlled
		25	LAM + ADV	
Wang, 2011 [96]	China	31	LAM + ADV	Prospective case–control
		40	ETV	
Berg, 2010 [97]	Multiple countries	52	FTC/TDF	Randomized, double-blind, double-dummy
		53	TDF	
Karino, 2010 [98]	Japan	82	ETV	Open-label, single-arm
Kim, 2010 [99]	Republic of Korea	24	ETV	Retrospective cohort
		44	ADV	
		36	ADV + LAM	
Kim, 2010 [100]	Republic of Korea	55	Clevudine	Retrospective cohort
		73	ETV	
Suh, 2010 [101]	Germany	23	LdT	Open-label, parallel-group, randomized (phase 3b)
	Republic of Korea	21	ETV	
Yokosuka, 2010 [8]	Japan	167	ETV	Open-label, single-arm
Zheng, 2010 [102]	China	65	LdT	Open-label randomized
		66	ETV	
Chang, 2009 [103]	Multiple countries	354	ETV	Randomized, double-dummy
		355	LAM	

Table 1 continued

Authors, year	Country	Patients (*n*)	Drugs	Study design
Kobashi, 2009 [104]	Japan	32	ETV 0.1	Randomized, double-blind
		34	ETV 0.5	
Liaw, 2009 [105]	Multiple countries	680	LdT	Randomized, double-blind, phase 3
		687	LAM	
Shindo, 2009 [106]	Japan	35	ETV 0.01 mg	Randomized, double-blind
		34	ETV 0.1 mg	
		34	ETV 0.5 mg	
		34	LAM 100 mg	
Yao, 2009 [107]	China	110	Placebo/LAM	Randomized, double-blind
		329	LAM/LAM	
Hou, 2008 [108]	China	167	LdT	Randomized, double-blind
		165	LAM	
Marcellin, 2008 [109]	Multiple countries	426	TDF	Randomized, double-blind, phase 3
		215	ADV	
Marcellin, 2008 [110]	Multiple countries	65	ADV	Open-label, single-arm *
Sung, 2008 [111]	Multiple countries	57	LAM	Randomized, double-blind
		54	LAM + ADV	
Suzuki, 2008 [112]	Japan	41	ETV 0.5	Randomized, double-blind
		43	ETV 1.0	
Chan, 2007 [113]	Multiple countries	45	LdT	Open-label trial
		44	ADV	
		46	ADV + LdT	
Gish, 2007 [114]	Multiple countries	355	LAM	Randomized, double-blind, double-dummy
		354	ETV	
Lai, 2007 [115]	Multiple countries	680	LdT	Randomized, double-blind, phase 3
		687	LAM	
Lim, 2007 [116]	Multiple countries Caucasian	142	ADV	Phase 3, randomized, double-blind, placebo controlled
		100	Placebo	
	Asian	138	ADV	Phase 3, randomized, double-blind, placebo controlled
		121	Placebo	
Rapti, 2007 [117]	Greece	14	ADV	randomized controlled study
		28	ADV + LAM	
Ren, 2007 [118]	China	21	LAM	Randomized controlled
		21	ETV 0.5 mg	
		19	ETV 1.0 mg	
Chang, 2006 [119]	Multiple countries	354	ETV	Double-blind, double-dummy, randomized, controlled
		355	LAM	
Hadziyannis, 2006 [120]	Multiple countries	125	ADV	Double-blind phase (96 weeks) + open-label safety and efficacy (144 weeks)
		62	Placebo	
Lai, 2006 [121]	Multiple countries	325	ETV	Randomized, double-blind, controlled
		313	LAM	
Sherman, 2006 [122]	Multiple countries	141	ETV	Randomized, double-blind, double-dummy, active controlled
		145	LAM	
Chan, 2005 [123]	China	50	PEGIFN ∝ -2b + LAM	Randomized, controlled, open-label
		50	LAM	

Table 1 continued

Authors, year	Country	Patients (*n*)	Drugs	Study design
Chang, 2005 [124]	Multiple countries	42	ETV 1.0	Randomized, dose-ranging, phase 2
		47	ETV 0.5	
		47	ETV 0.1	
		45	LAM	
Lai, 2005 [125]	Multiple countries	19	LAM	Double-blind, randomized, phase 2b
		22	LdT 400 mg	
		22	LdT 600 mg	
		21	LAM + LdT 400 mg	
		20	LAM + LdT 600 mg	
Lau, 2005 [126]	Multiple countries	271	PEGIFN ∝ -2a	Randomized, partially double-blind
		271	PEGIFN ∝ -2a + LAM	
		272	LAM	
Rizzetto, 2005 [127]	Multiple countries	76	LAM	Open-label prospective
Sarin, 2005 [128]	India	38	IFN ∝ -2 + LAM	Randomized open-label
		37	LAM	
Liaw, 2004 [129]	Asia, Australia, United Kingdom	436	LAM	Randomized, double-blind, placebo-controlled, parallel group
		215	Placebo	
Marcellin,2004 [130]	Asia, Europe	177	PEGIFN ∝ -2a	Randomized, partially double-blind
		179	PEGIFN ∝ -2a + LAM	
		181	LAM	
Yao, 2004 [131]	China	322	LAM	Randomized, double-blind, placebo controlled
		107	Placebo	
Ali, 2003 [132]	Iraq	32	LAM	Randomized, placebo controlled
		30	Placebo	
Dienstag, 2003 [133]	Multiple countries	40	LAM	Unblinded, observational
Dienstag, 2003 [134]	Canada, USA, England	63	LAM	Open label, prospective
Marcellin, 2003 [135]	Multiple countries	168	ADV 10 mg	Randomized, phase 2
		165	ADV 30 mg	
		161	Placebo	
Schiff, 2003 [136]	Multiple countries	119	LAM	Randomized, partially blinded
		63	LAM + IFN ∝ -2b	
		53	Placebo	
Lai, 2002 [137]	Multiple countries	54	ETV 0.01 mg	Randomized, double-blind, dose-ranging
		36	ETV 0.1 mg	
		46	ETV 0.5 mg	
		41	LAM 100 mg	
Lai, 2002 [138]	China	50	LAM	Randomized, prospective
		50	Famciclovir	
Mazur, 2002 [139]	Poland	45	LAM	Open-label, prospective
Da Silva, 2001 [140]	Brazil	32	LAM	Open- label, prospective

Table 1 continued

Authors, year	Country	Patients (*n*)	Drugs	Study design
de Man, 2001 [141]	Multiple countries	8	ETV 0.05 mg	Randomized, placebo-controlled, dose-escalating
		9	ETV 0.1 mg	
		9	ETV 0.5 mg	
		8	ETV 1.0 mg	
		8	Placebo	
Leung, 2001 [142]	China	58	LAM	Open-label, prospective
Montazeri, 2001 [143]	Iran	18	LAM	Randomized, open-label
		18	LAM + IFN ∝	
Hadziyannis, 2000 [144]	Greece	25	LAM	Open-label, single-arm, prospective
Lau, 2000 [145]	USA	27	LAM	Open-label trial, single-arm, prospective
Liaw, 2000 [146]	China	31	LAM 25 mg + placebo	Randomized, double-blind, placebo controlled
		101	LAM 25 mg + LAM 25 mg	
		41	LAM 100 mg + placebo	
		93	LAM 100 mg + LAM 100 mg	
Santantonio, 2000 [147]	Italy	15	LAM	Open-label, single-arm, prospective
Yao, 2000 [148]	China	107	Placebo + LAM	Randomized double-blind placebo controlled
		322	LAM + LAM	
Dienstag, 1999 [149]	USA	66	LAM	Prospective, randomized, double-blind, placebo controlled
		71	Placebo	
Gilson, 1999 [150]	United Kingdom	15	ADV	Randomized, double-blind, placebo controlled, phase I/II
		5	Placebo	
Tassopoulos, 1999 [151]	Multiple countries	60	LAM	Placebo controlled, double-blind, randomized
		64	Placebo	
Lai, 1998 [152]	China	143	LAM 100 mg	Randomized, double-blind
		142	LAM 25	
		72	Placebo	
Lai, 1997 [153]	China	12	LAM 25 mg	Randomized, placebo controlled
		12	LAM 100 mg	
		12	LAM 300 mg	
		6	placebo	
Nevens, 1997 [154]	Europe	16	LAM 25 mg	Randomized, partially double-blind
		16	LAM 100 mg	
		19	LAM 300 mg	
Dienstag, 1995 [155]	USA	10	LAM 25 mg	Double-blind trial
		11	LAM 100 mg	
		11	LAM 300 mg	

ADV (adefovir dipivoxil); ETV (entecavir); FTC (emtricitabine); IFN (interferon); LAM (lamivudine); LdT (telbivudine); TDF (tenofovir disoproxil fumarate); TAF (tenofovir alafenamide)

* LTSES (long-term safety and efficacy study)

Table 2 Frequency of AEs reported according to the drug

	LAM	ETV	LdT	ADV	TDF	TAF
Studies	49	35	19	10	26	3
Patients	6419	5947	3096	1178	3566	876
AEs	5554	1086	2302	1426	837	998
AEs/patients[a]	0.87	0.18	0.74	1.2	0.23	1.14
Blood and lymphatic systems disorders	20 (0.4%)	3 (0.3%)	22 (1%)	8 (0.6%)	9 (1.1%)	–
Cardiac disorders	7 (0.1%)	6 (0.6%)	1 (0.1%)	–	–	–
Ear and labyrinth disorders	5 (0.1%)	1 (0.1%)	–	1 (0.1%)	–	–
Endocrine disorders	–	–	1 (0.1%)	–	1 (0.1%)	–
Eye disorders	–	1 (0.1%)	6 (0.3%)	1 (0.1%)	–	–
Gastrointestinal disorders	**1116 (20.1%)**	**102 (9.4%)**	**405 (17.6%)**	**244 (17.1%)**	**128 (15.3%)**	**227 (22.7%)**
General disorders	**811 (14.6%)**	**77 (7.1%)**	**214 (9.3%)**	157 (11%)	**82 (9.8%)**	53 (5.3%)
Hepatobiliary disorders	66 (1.2%)	–	–	–	9 (1.1%)	–
Infections and infestations	**871 (15.7%)**	**231 (21.3%)**	**650 (28.2%)**	**260 (18.2%)**	**110 (13.1%)**	**175 (17.5%)**
Laboratory abnormalities	650 (11.7%)	**218 (20.1%)**	**347 (15.1%)**	**179 (12.6%)**	**157 (18.8%)**	**202 (20.2%)**
Metabolism and nutrition disorders	–	–	1 (0.1%)	–	6 (0.7%)	19 (1.9%)
Musculoskeletal and connective tissue disorders	171 (3.1%)	24 (2.2%)	186 (8.1%)	109 (7.6%)	30 (3.6%)	25 (2.5%)
Neoplasms	14 (0.3%)	11 (1%)	7 (0.3%)	–	7 (0.8%)	–
Nervous system disorders	**669 (12%)**	**193 (17.8%)**	**254 (11%)**	**216 (15.1%)**	**66 (7.9%)**	**86 (8.6%)**
Psychiatric disorders	73 (1.3%)	2 (0.2%)	1 (0.1%)	–	4 (0.5%)	–
Renal and urinary disorders	1 (0.02%)	17 (1.6%)	2 (0.1%)	6 (0.4%)	57 (6.8%)	**111 (11.1%)**
Reproductive system disorders	1 (0.02%)	1 (0.1%)	–	–	–	–
Respiratory disorders	**696 (12.5%)**	19 (1.7%)	140 (6.1%)	**200 (14%)**	21 (2.5%)	54 (5.4%)
Skin and subcutaneous tissue disorders	47 (0.7%)	2 (0.2%)	–		15 (1.8%)	–
Serious AEs	271 (4.9%)	131 (12.1%)	53 (2.3%)	39 (2.7%)	82 (9.8%)	37 (3.7%)
Drug discontinuation	62 (1.1%)	33 (3%)	11 (0.5%)	2 (0.1%)	47 (5.6%)	9 (0.9%)
Death	3 (0.1%)	9 (0.8%)	1 (0.1%)	–	4 (0.5%)	–

In each column, the five AEs most often reported were scored in bold. The percentage in parentheses refers to the percentage relative to the total number of AEs reported in each drug

ADV adefovir dipivoxil, *AEs* adverse events, *ETV* entecavir, *LAM* lamivudine, *LdT* telbivudine, *TDF* tenofovir disoproxil fumarate, *TAF* tenofovir alafenamide

[a]Mean number of adverse events per treated patient

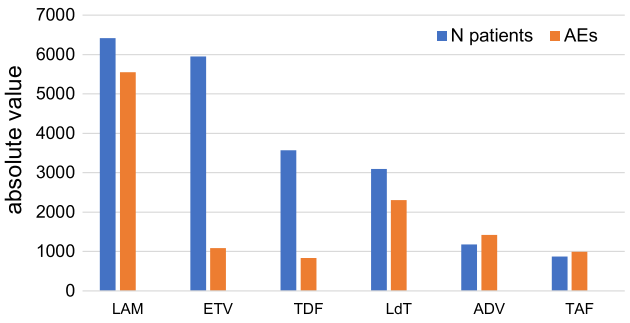

Fig. 2 Number of patients treated and absolute value of adverse events reported for each drug. *LAM* lamivudine, *ETV* entecavir, *TDF* tenofovir disoproxil fumarate, *LdT* telbivudine, *ADV* adefovir dipivoxil, *TAF* tenofovir alafenamide

The most noticed neurological event was headache (n = 509). Regarding respiratory problems, viral respiratory infections were the most reported (n = 177).

Hepatic enzyme increase was the most documented laboratory abnormality (n = 473).

Although rhabdomyolysis was not described, 70 cases of elevated creatine kinase (CK) were documented, but did not lead to drug withdrawal.

Entecavir (ETV)

In the studies using ETV (0.5 or 1.0 mg), a total of 1086 AEs were reported (0.18 AE/patient treated) [Fig. 2, Table 2].

Table 3 Mean percentage decrease in hip and spine bone mineral density with TDF and TAF in studies comparing the two drugs

Study	Follow-up		TAF	TDF	p
Buti, 2016 [29]	48 weeks	hip	− 0.29%	− 2.16%	< 0.0001
		spine	− 0.88%	− 2.51%	0.0004
Chan, 2016 [30]	48 weeks	hip	− 0.1%	− 1.72%	< 0.0001
		spine	− 0.42%	− 2.29%	< 0.0001

Table 4 Mean increase in serum creatinine (Cr) from baseline and the median decrease in estimated glomerular filtration rate (eGFR) with TDF and TAF in studies comparing the two drugs

Study	Follow-up		TAF	TDF	*p*
Buti, 2016 [29]	48 weeks	↑Cr (mg/dl)	0.01	0.02	0.32
		↓eGFR (ml/min)	1.8	4.8	0.004
Chan, 2016 [30]	48 weeks	↑Cr (mg/dl)	0.01	0.03	0.02
		↓eGFR (ml/min)	0.6	5.4	< 0.0001

The most frequent AEs reported were infections and infestations (21.3%), laboratory abnormalities (20.1%), nervous system disorders (17.8%), gastrointestinal disorders (9.4%) and general disorders (7.1%) [Table 2].

Nasopharyngitis was the most frequent infection (n = 210). Regarding laboratory abnormalities, ALT elevation was the most reported (n = 117).

Headache corresponded to 95% of the nervous system disorders (n = 185). Among gastrointestinal disorders, diarrhea was the most common (n = 62). Of the general disorders, fatigue was the most reported (n = 71). CK elevation has been described in 49 patients.

Telbivudine (LdT)

In the studies using LdT (600 mg), a total of 2302 AEs were reported (0.74 AE/patient treated) [Fig. 2, Table 2].

The most frequent AEs reported were infections and infestations (28.2%), gastrointestinal disorders (17.6%), laboratory abnormalities (15.1%), nervous system disorders (11%) and general disorders (9.3%) [Table 2].

Nasopharyngitis was the most frequent infection (n = 295). Among gastrointestinal disorders, diarrhea was the most common (n = 114). Regarding laboratory abnormalities, CK elevation was the most reported (n = 211).

Headache corresponded to 72% of the nervous system disorders (n = 183). Of the general disorders, fatigue was the most reported (n = 71).

Adefovir dipivoxil (ADV)

A total of 1426 AEs was documented in studies with 10 mg of ADV (1.2 AE/treated patient) [Fig. 2, Table 2].

The most frequent AEs reported were infections and infestations (18.2%), gastrointestinal disorders (17.1%), nervous system disorders (15.1%), respiratory disorders (14%) and laboratory abnormalities (12.6%).

Nasopharyngitis was the most frequently described infection (n = 181). Regarding gastrointestinal disorders, the most common was abdominal pain (n = 115). Among neurological alterations, headache was the most described (n = 185). Regarding respiratory problems, flu syndrome was the most reported (n = 96).

ALT elevation was the most frequently described laboratory abnormality (n = 90).

CK elevation has been described in 22 patients.

Tenofovir disoproxil fumarate (TDF)

A total of 837 AEs were documented in studies with 300 mg of TDF (0.23 AE/treated patient) [Fig. 2, Table 2].

The most frequent AEs reported were laboratory abnormalities (18.8%), gastrointestinal disorders (15.3%), infections and infestations (13.1%), general disorders (9.8%) and nervous system disorders (7.9%).

Creatinine elevation was the most frequently described laboratory abnormality (n = 30). Regarding gastrointestinal disorders, the most common was nausea (n = 44). Nasopharyngitis was the most frequently described infection (n = 51). Fatigue was the most reported symptom in the general disorders section (n = 44).

Among neurological alterations, headache was the most described (n = 54). CK elevation has been described in 13 patients.

When evaluating renal and urinary disorders, 24 cases of urine erythrocytes and 2 cases of urine glucose were reported.

Tenofovir alafenamide (TAF)

A total of 998 AEs were reported in studies with 25 mg TAF (1.14 AE/treated patient) [Fig. 2, Table 2].

The most frequent AEs reported were gastrointestinal disorders (22.7%), laboratory abnormalities (20.2%),

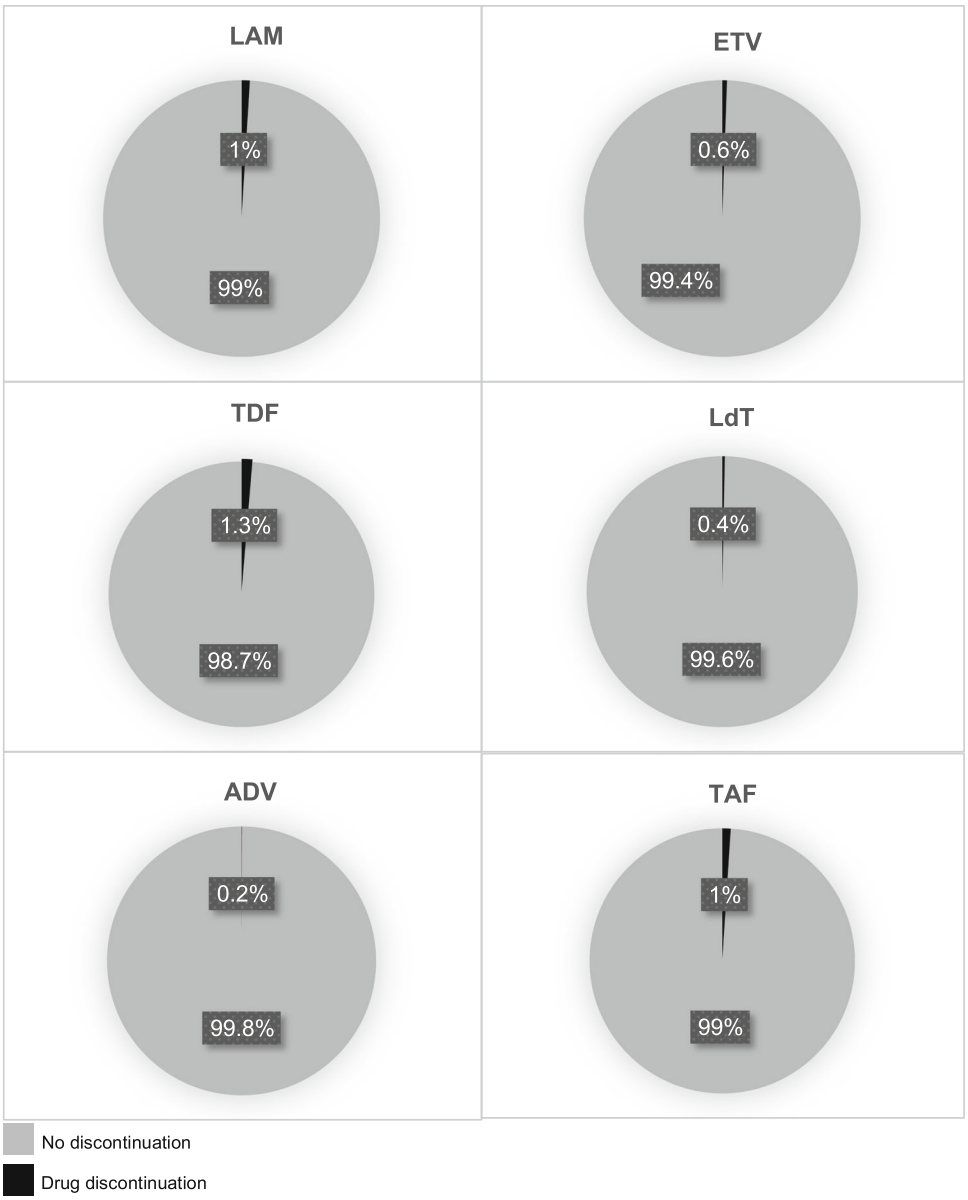

Fig. 3 Percentage of drug discontinuation due adverse events for each nucleos(t)ide analogue. *LAM* lamivudine, *ETV* entecavir, *TDF* tenofovir disoproxil fumarate, *LdT* telbivudine, *ADV* adefovir dipivoxil, *TAF* tenofovir alafenamide

infections and infestations (17.5%), renal and urinary disorders (11.1%) and nervous system disorders (8.6%).

Regarding gastrointestinal disorders, the most common finding was occult blood in stool ($n = 63$). Among the laboratory abnormalities, the most reported were elevated ALT ($n = 75$) and elevated LDL cholesterol ($n = 35$). Nasopharyngitis was the main infections described ($n = 89$). Concerning the renal/urinary changes, urine erythrocytes ($n = 68$) and urine glucose ($n = 43$) were reported.

Headache was the most reported neurological disorder ($n = 84$). Elevation of CK has been described in 23 patients.

TDF versus TAF

Tables 3 and 4 summarized data on AEs on bone density and renal disorders, respectively, from two studies comparing TDF and TAF.

With regard to bone density, TDF caused greater bone loss in both hip and spine compared to TAF [Table 3].

On the other hand, when analysing the renal AEs, there was no clinically significant difference between the two drugs regarding the elevation of serum creatinine, but there was a greater reduction in the glomerular filtration rate in patients who received TDF [Table 4].

Drug discontinuation due adverse events

In the studies analysed, the percentage of drug discontinuation with LAM, ETV, TDF, LdT, ADV and TAF were, respectively, 1% (*n*. 62), 0.6% (*n*. 33), 1.3% (*n*. 47), 0.4% (*n*. 11), 0.2% (*n*. 2) and 1% (*n*. 9) [Fig. 3].

Discussion

The aim of CHB treatment was to control viral replication, thereby reducing the risk of complications such as liver failure, cirrhosis and hepatocellular carcinoma. CHB treatment is often based on long-term NAs use, with the following drugs being approved: LAM, ETV, LdT, ADV, TDF and TAF, of which ETV, TDF and TAF are considered to be first-line drugs, due to its potency and high genetic barrier to resistance. Identification of potential associated AEs, even if with low incidence, might be a key factor in improving adherence and outcomes. We performed a systematic literature review of studies that included LAM, ETV, LdT, ADV, TDF and TAF since 1990 and extracted all of the reported AEs from them.

One must be aware upon reading this review, there is no necessarily causation between documented AEs and pharmacological treatment [11]. As hepatitis B infection itself may lead to extrahepatic organ involvement [12], it might be difficult to determine whether extrahepatic manifestations/symptoms are treatment-related or a disease manifestation.

Data collected in this systematic review corroborate with the understanding that serious AEs are rare within the use of NAs. The most common AEs in all NAs assessed were abdominal pain/discomfort, nasopharyngitis/upper respiratory tract infections, fatigue and headache. These symptoms are not uncommon in the general population and, perhaps, these findings are related to their high prevalence among the general population rather than to drug treatment itself.

Extrahepatic AEs may result from mitochondrial toxic effect of NAs [13]. They suppress viral replication by the inhibition of the HBV polymerase enzyme. As NA structures are similar to natural nucleosides, some of these agents can also inhibit human mitochondrial polymerase-γ and cause mitochondrial toxicity [12, 14, 15]. Mitochondrial toxicity was first noticed during HIV treatment with highly active antiretroviral therapy. Because NAs lead to a minimal mitochondrial polymerase-γ inhibition, NAs associated mitochondrial toxicity cases have been rarely reported. All NAs carry a warning of mitochondrial toxicity as part of their prescribing information [12, 14, 15]. Clinical manifestations of mitochondrial toxicity include hematologic disorders, peripheral neuropathy, skeletal and cardiac myopathy, pancreatitis, hepatic failure and lactic acidosis [13, 14, 16]. Among the few AE reported in studies of this systematic review, those that could be correlated to mitochondrial toxicity are CK elevation (70 cases with LAM, 49 with ETV, 211 with LdT, 22 with ADV, 13 with TDF and 23 with TAF)—but without clinical repercussion that required drug suspension; and one case of ETV-related pancreatitis.

Tenofovir disoproxil fumarate (TDF) is a prodrug of tenofovir that was approved as a NA by the United States FDA for use in CHB infection in 2008. TDF is converted to tenofovir by hydrolysis and then phosphorylated by cellular enzymes to tenofovir diphosphate [13]. It is a highly potent inhibitor of HBV DNA replication and recommended as a first-line treatment choice in CHB by the current clinical guidelines due to the absence of drug resistance [17] [18]. Tenofovir has been shown to have a potential nephrotoxic effect in patients with HIV infection who were treated for an especially extended period. However, in clinical trials, nephrotoxicity does not seem to be a major problem in HBV monoinfection [15]. Increases in serum creatinine of > 0.5 mg/dL were reported to be detected in 1% of patient [19]. Another AE concern within TDF use is the bone mass reduction. In randomized clinical trials, a great loss of bone mineral density (BMD) had been well-described in patients with HIV infection treated with TDF [20] [21, 22]. However, tenofovir-related bone fractures were not reported in patients with HBV monoinfection [20]. The exact mechanism of bone toxicity in CHB is not clear. For example, the prevalence of BMD loss in patients receiving tenofovir was similar to those who were not exposed to tenofovir. Tenofovir was reported to be associated with a lower T score only in the hips. Additionally, in this study there was no significant correlation between duration of exposure to tenofovir and reduction in BMD at any side. Additionally, a large retrospective study in Hong Kong demonstrated that BMD reduction remains stable on a plateau from year 4 through year 7 of tenofovir treatment, for both hip and lumbar spine [23]. These data indicate that loss of bone mass is not a progressive event with the use of TDF.

A pro-drug formulation, tenofovir alafenamide (TAF), was recently launched in North America and Europe, being approved for the treatment of CHB in 2016 by the FDA (Food and Drug Administration). The pharmacokinetics of TAF leads to a 6.5-times higher intracellular concentration of the phosphorylated moiety tenofovir diphosphate, and 91% lower serum concentration of tenofovir, compared to TDF [24–26]. Given these pharmacokinetic differences, TAF dose can be far lower: a 25-mg once-daily dose of TAF is bioequivalent to TDF at 300-mg once daily, in terms of tenofovir plasma. Pharmacodynamic studies suggest that the lower tenofovir concentrations in plasma

produced by TAF translate to reduced off-target drug exposure, for example, in the kidneys and bones, with implications regarding AEs [27]. TAF is, therefore, predicted to confer the same clinical efficacy as TDF, with potential improvements in its tolerability [27, 28].

In Tables 1 and 2 of this review, we report the results of two studies comparing TDF and TAF (Buti et al. and Chan et al.) [29, 30] concerning renal and bone alteration. The study by Buti et al. had a follow-up of 3 years and Chan et al. had a follow-up of 48 weeks. Both studies suggest that the bone density reduction was greater with the use of TDF, although no drug-related fractures were described. The same occurred with glomerular filtration rate, also with a greater reduction in the groups that received TDF. With these data, we raised two main questions: (1) what is the exact clinical repercussion of these findings? (2) Will such changes remain stable or continue to progress over the years?

Interestingly, renal/urinary changes were the 4th most reported group of AEs among patients on TAF, while the 6th for TDF and the 8th and 12th for ETV and LAM, respectively. Regarding reports for TAF in this group of AEs, there were 43 cases of glycosuria (versus 2 cases with TDF) and 68 cases of urine erythrocytes (versus 24 with TDF). At this time, we do not know the clinical relevance of these findings and whether they may represent any indication of renal tubular damage. Also, the number of patients treated with TAF is markedly lower than the number of patients who received the other NAs. Yet, TAF displays the highest proportion of AEs per patient treated among NAs.

These data fortify the idea that perhaps the greater safety of TAF in relation to TDF may have been overestimated, as already mentioned in the Hill et al. meta-analysis, which compared both drugs in HIV and CHB therapy [31].

It is known that susceptibility to AEs may vary by population. Previously, cases of Fanconi syndrome due to long-term use of adefovir have been reported using adefovir, with a higher incidence in East Asian populations [32]. However, in this review, the incidence of AEs according to ethnicity could not be differentiated. We believe that the low incidence of AEs from NAs makes this differentiation difficult.

Another important point to highlight is that the efficacy of treatments for CHB can be affected by a number of factors, including the development of AEs and poor patient compliance. In fact, a significant number of virological breakthrough may be related to medication nonadherence [33]. Hongthanakorn et al. analysed 148 patients with CHB and demonstrated that 38% of patients who experienced virological breakthrough were not confirmed to have antiviral resistance mutations, suggesting that medication nonadherence may be the cause of the virological breakthrough in these patients [34].

In this review, all drugs had a small percentage of discontinuation due to AEs, which is consistent with the literature. For example, Suzuki et al. reported that 1.3% of patients who were treated with ETV discontinued NA therapy because of AEs. Another study that evaluated LAM, LdT and ETV during the 3-year period found that patients with ETV had the best adherence [35]. This result strengthens the idea of ETV as one of the first-line agents in the treatment of CHB. Nevertheless, it should be emphasized that poor adherence, often still neglected, can have a negative effect on the treatment of chronic hepatitis B, with inadequate viral suppression, increased incidence of cirrhosis and hepatocellular carcinoma, and potential emergence of NAs-resistant [36, 37]. The situation of HBV resistance to NAs in some countries is severe and, to prevent emergence of resistance, NAs with the lowest rate of genotypic resistance should be administered (TDF, TAF or ETV) and adherence reinforced [33, 36–38].

Conclusion

Treatment of CHB with NAs is safe, with a low incidence of adverse events. The most common AEs with all drugs are abdominal pain/discomfort, nasopharyngitis/upper respiratory tract infections, fatigue and headache. TDF demonstrated a greater reduction in the glomerular filtration rate and bone density of the lumbar spine and hips when compared to TAF. Currently, the number of patients treated with TAF still is too small to consolidate that TAF is really safer than TDF.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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