**Appendix 1. Search strategy**

**PubMed**

#1 entecavir[tiab] OR baraclude[tiab] OR adefovir[tiab] OR “adefovir dipivoxil”[tiab] OR preveon[tiab] OR hepsera[tiab] OR telbivudine[tiab] OR sebivo[tiab] OR tyzeka[tiab] OR tenofovir[tiab] OR “tenofovir disoproxil fumarate”[tiab] OR viread[tiab] OR“tenofovir alaninamide fumarate”[tiab] OR lamivudine[tiab] OR epivir[tiab] OR heptodin[tiab] OR heptodine[tiab] OR nucleoside analogue[tiab] OR nucleotide analogue[tiab]

#2 hepatitis B[tiab] OR HBV[tiab] OR HBsAg[tiab] OR Hepatitis B Surface Antigens[tiab] OR hepatitis B[MeSH Terms] OR Hepatitis B Surface Antigens[MeSH Terms]

#3 randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]

#4 animals [mh] NOT humans [mh]

#5 #3 NOT #4

#6 #1 AND #2 AND #5

**Embase**

#1 randomized controlled trial.ab.

#2 controlled clinical trial.ab.

#3 randomized.ab.

#4 placebo.ab.

#5 drug therapy.fs.

#6 (random or randomly).ab.

#7 trial.ab.

#8 groups.ab.

#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8

#10 (animal or nonhuman).mp. not (human and (animal or nonhuman)).de. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

#11 9 not 10

#12 hepatitis B.sh. or Hepatitis B Surface Antigens.sh. or hepatitis B.ab. or HBV.ab. or HBsAg.ab. or Hepatitis B Surface Antigens.ab.

#13 nucleos(t)ide analogues (‘entecavir’, ‘adefovir’, ‘telbivudine’, ‘tenofovir’, ‘lamivudine’).

#14 entecavir.ab. or baraclude.ab. or adefovir.ab. or adefovir dipivoxil.ab. or preveon.ab. or hepsera.ab. or telbivudine.ab. or sebivo or tyzeka or tenofovir.ab. or tenofovir disoproxil fumarate.ab. or viread.ab. or tenofovir alafenamide fumarate.ab. or tenofovir alafenamide.ab. or lamivudine.ab. or amilitrap.ab. or antiheb.ab. or avilam.ab. or avolam.ab. or epivir-HBV.ab. or flamivud.ab. or ganvirel.ab. or hepavir.ab. or hepitec.ab. or heptavir.ab. or heptodin.ab. or heptodine.ab. or lamda.ab. or lamibergen.ab. or lamidac.ab. or lamitec.ab. or lamivir.ab. or zeffix.ab. or nucleoside analogue.ab. or nucleotide analogue.ab.

#15 #11 and #12 and (#13 or #14)

**Cochrane Central Register of Controlled Trials (CENTRAL)**

#1 entecavir OR baraclude OR adefovir OR adefovir dipivoxil OR telbivudine OR sebivo OR tenofovir OR tenofovir disoproxil fumarate OR viread OR tenofovir alaninamide fumarate OR lamivudine OR epivir OR heptodin OR heptodine: ti, ab, kw

#2 hepatitis B or Hepatitis B Surface Antigens or hepatitis B or HBV or HBsAg or Hepatitis B Surface Antigens: ti, ab, kw

#3 #1AND #2

**Science Citation Index Expanded (Web of Science)**

#1 TS=(entecavir OR baraclude OR adefovir OR “adefovir dipivoxil” OR telbivudine OR sebivo OR tenofovir OR “tenofovir disoproxil fumarate” OR viread OR“tenofovir alaninamide fumarate” OR lamivudine OR epivir OR heptodin OR heptodine)

#2 TS=(hepatitis B or Hepatitis B Surface Antigens or hepatitis B or HBV or HBsAg or Hepatitis B Surface Antigens)

#3 TS=(randomized OR clinical trial [pt] OR randomised OR random OR randomly OR RCT)

#4 TS=(rabbit OR rat OR mice OR mouse OR animal)

#5 #3 NOT #4

#6 #1 AND #2 AND #5

**Wanfang Data**

(摘要:('恩替卡韦'+'博路定'+'阿德福韦'+'阿德福韦酯'+'贺维力'+'替比夫定'+'素比伏'+'替泽卡'+'替诺福韦'+'替诺福韦酯'+'韦瑞德'+'拉米夫定'+'拉米夫啶'+'拉米呋啶'+'贺普丁'+'益平维'+'贺甘定'+'健甘灵'+'万生力克'+'核苷'+'核苷酸'))\* (摘要:('随机') + 题名或关键词:('随机')) \* (摘要'乙型肝炎'+'乙肝'+HBV) ^ 题名或关键词: ('系统评价'+'荟萃'+'Meta'+'综述'+'进展'+'回顾'+'病例对照'+'队列研究'+'鼠'+'兔'+'动物')

**VIP Chinese Science and Technique Journals Database**

(R='恩替卡韦'-'博路定'-'阿德福韦'-'阿德福韦酯'-'贺维力'-'替比夫定'-'素比伏'-'替泽卡'-'替诺福韦'-'替诺福韦酯'-'韦瑞德'-'拉米夫定'-'拉米夫啶'-'拉米呋啶'-'贺普丁'-'益平维'-'贺甘定'-'健甘灵'-'万生力克'-'核苷'-'核苷酸'))\* (R:('随机') + M:('随机')) \* (摘要'乙型肝炎'+'乙肝'+HBV) ^ M: ('系统评价'+'荟萃'+'Meta'+'综述'+'进展'+'回顾'+'病例对照'+'队列研究'+'鼠'+'兔'+'动物')

**China National Knowledge Infrastructure (CNKI)**

AB = ('乙型肝炎'+'乙肝'+HBV) and AB =('恩替卡韦'+'博路定'+'阿德福韦'+'阿德福韦酯'+'贺维力'+'替比夫定'+'素比伏'+'替泽卡'+'替诺福韦'+'替诺福韦酯'+'韦瑞德'+'拉米夫定'+'拉米夫啶'+'拉米呋啶'+'贺普丁'+'益平维'+'贺甘定'+'健甘灵'+'万生力克'+'核苷'+'核苷酸') and (AB ='随机' or TI ='随机' or KY ='随机') not TI =('系统评价'+'荟萃'+'Meta'+'综述'+'进展'+'回顾'+'病例对照'+'队列研究'+'鼠'+'兔'+'动物')

**Appendix 2. Codes for WinBUGS to conduct network meta-analysis**

//HBeAg seroconversion as an example

model

{

for (i in 1:ns)

{

w[i,1]<-0

delta[i,1]<-0

mu[i]~dnorm(0,0.0001)

for(k in 1:na[i])

{

r[i,k]~dbin(p[i,k],n[i,k])

logit(p[i,k])<-mu[i]+d[t[i,k]]-d[t[i,1]]

rhat[i,k]<-p[i,k]\*n[i,k]

dev[i,k]<-2\*(r[i,k]\*(log(r[i,k])-log(rhat[i,k]))+(n[i,k]-r[i,k])\*(log(n[i,k]-r[i,k])-log(n[i,k]-rhat[i,k])))

}

resdev[i]<-sum(dev[i,1:na[i]])

for(k in 2:na[i])

{

delta[i,k]~dnorm(md[i,k],taud[i,k])

md[i,k]<-d[t[i,k]]-d[t[i,1]]+sw[i,k]

taud[i,k]<-tau\*2\*(k-1)/k

w[i,k]<-(delta[i,k]-d[t[i,k]]+d[t[i,1]])

sw[i,k]<-sum(w[i,1:k-1])/(k-1)

}

}

totresdev<-sum(resdev[])

d[1]<-0

for(k in 2:nt)

{

d[k]~dnorm(0,0.0001)

}

sd~dunif(0,5)

tau<-pow(sd,-2)

for (c in 1:(nt-1))

{

for(k in (c+1):nt)

{

lrr[c,k]<-d[c]-d[k]

rr[c,k]<-exp(lrr[c,k])

}

}

for(k in 1:nt)

{

rk[k]<-nt+1-rank(d[],k)

best[k]<-equals(rk[k],1)

}

}

list(ns=31,nt=6)

r[,1] n[,1] r[,2] n[,2] t[,1] t[,2] na[]

9 167 20 171 6 1 2

19 108 7 53 3 6 2

0 19 2 19 3 1 2

2 59 2 32 2 3 2

16 344 1 116 1 6 2

74 354 64 355 2 3 2

11 141 4 145 2 3 2

7 44 9 89 4 1 2

33 225 39 221 2 3 2

32 153 14 80 5 1 2

5 36 7 33 2 1 2

136 458 114 463 4 3 2

1 28 1 30 2 3 2

13 39 5 41 2 1 2

25 90 13 90 4 2 2

8 22 7 24 2 3 2

1 15 2 15 3 1 2

12 81 8 81 4 3 2

1 35 3 34 3 2 2

15 39 13 23 3 1 2

40 138 28 138 4 3 2

2 7 0 8 5 1 2

16 103 9 99 2 3 2

9 38 5 35 5 2 2

11 45 15 66 4 2 2

59 95 36 93 4 2 2

12 38 5 38 4 2 2

0 40 2 33 2 5 2

26 95 31 92 5 2 2

5 60 4 56 5 2 2

4 43 2 27 4 1 2

END

list(d=c(NA,0,0,0,0,0),sd=1,mu=c(0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0))

list(d=c(NA,-1,-1,-1,-1,-1),sd=4,mu=c(-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3))

list(d=c(NA,2,2,2,2,2),sd=2,mu=c(-4,-4,-4,-4,-4,-4,-4,-4,-4,-4,-4,-4,-4,-4,-4,-4,-4,-4,-4,-4,-4,-4,-4,-4,-4,-4,-4,-4,-4,-4,-4))

**Appendix 3. Flow diagram of search results**

Records identified through database searching (n=17,907)

Records after duplicates removed (n=9,691)

Duplicate records excluded (n=8,216)

Records excluded after reading title and abstracts (n=9,206)

* Not relevant to NMA topic (n=5,166)
* Non-RCTs (n=873)
* Not monotherapy (n=1,023)
* Not including participants (n=547)
* Not including interventions (n=667)
* Not including comparisons (n=295)
* Conference abstract, review, meta-analysis, comment (n=635)

Full-text articles assessed for eligibility (n=485)

Studies included in NMA (n=36)

Full text articles excluded (n=434)

* Not relevant to NMA topic (n=303)
* Non-RCTs (n=47)
* Not monotherapy (n=15)
* Duplicate data for the same study period (n=13)
* No available data (n=20)
* Not including participants (n=34)
* Not including comparisons (n=17)

Supplemental Figure 1. Flow diagram of the search results

**Appendix 4. Characteristics of included studies**

Supplementary Table 1. Characteristics of the included studies

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| ID | Setting | Clinical Trial Registration | Funding/Support//Several authors worked for pharmaceutical companies | Intervention | Baseline characteristics |
| Age (years) | HBV DNA(log10 IU/ml) | ALT(U/L) | HBeAg | Exclusion of prior nucleos(t)ide therapy for more than 12 weeks | Duration of treatment | Outcome measures |
| Marcellin P 2003[34] | 78 centers in North America, Europe, Australia, and Southeast Asia | — | Yes | ADFPlacebo | 34±11.237±11.8 | 8.25±0.908.12±0.89 | 139±154139 ± 131 | P | Yes | 48 weeks | HBeAg seroconversion; HBeAg loss; ALT normalization;Undetectable HBV DNA  |
| Schiff ER 2003[35] | 63 centers in 11 countries | — | Yes | LAMPlacebo | 37 (15–70)35 (18–64) | Median 111 (UD–1668)(pg/ml)80 (UD–1150) | △Median 2.8 (0.9–23.4)2.2 (0.8–14.4) | P | No | 52 weeks | HBeAg seroconversion; HBeAg loss;Undetectable HBV DNA |
| Yao GB 2003[36] | 5 centers in China | — | Yes | LAMPlacebo | 16-65\* | — | — | P | Yes | 12 weeks | ALT normalization; Undetectable HBV DNA |
| Peters MG 2004[37] | 20 centers in 6 countries | — | Yes | LAMADF | Median44, 33-69Median45, 26-64 | Median8.20, 6.08–8.82Median8.42,7.30–9.21 | Median 70Median 101 | P | No | 48 weeks | HBeAg seroconversion; ALT normalization’ Undetectable HBV DNA |
| Chang TT 2005[38] | 41 centers in 14 countries | — | Yes | ETV 1.0mg/dETV 0.5mg/dLAM | 48±1344±1348±15 | 9.07± 1.549.29± 0.829.28 ± 0.82 | 141 ± 186113± 116110± 97 | B | No | 48 weeks | HBeAg seroconversion; HBeAg loss; ALT normalization; Undetectable HBV DNA;SAE |
| Lai CL 2005[39] | 16 clinical centers in 5 countries | — | Yes | LAMLTD | Median 34, 18-61Median 40, 19–60 | Median 9.3, 6.6–12.9Median 9.0, 6.3–13.3 | Median 122, 62–309Median 130, 61–325 | P | Yes | 52 weeks | ALT normalization |
| Zeng MD 2005[40] | 12 hospitals in 5 cities in China | — | Yes | ADFPlacebo | AAA: 31±9; AAP: 32±10PAA: 32±10 | AAA: 8.6±1.0; AAP:8.5±1.0PAA:8.6±1.0 | △AAA: 3.9±3.8; AAP:3.3±2.6PAA:3.8±4.1 | P | No | 12 weeks▲ | HBeAg seroconversion; HBeAg loss; ALT normalizationUndetectable HBV DNA |
| Chang TT 2006[41] | 41 centers in North America, Asia , Australia, and South America | NCT00035633 | Yes | ETV 0.5mg/dLAM | 35±1335±13 | 9.62±2.019.69±1.99 | 140.5±114.3146.3±132.3 | P | Yes | 48 weeks | HBeAg seroconversion; HBeAg loss; ALT normalization; Undetectable HBV DNA; SAE |
| Lai CL 2006[42] | 146 centers in Europe, the Middle East, Asia, Australia, North America, and South America | NCT00035789 | Yes | ETV 0.5mg/dLAM | 41±1141±11 | 7.6±1.87.6±1.7 | 141±114.7143±119.4 | N | Yes | 48 weeks | ALT normalization; Undetectable HBV DNA; SAE; HCC incidence |
| Sherman M 2006[43] | 84 sites in North America, South America, Europe and the Middle East, Australia, and Asia | — | Yes | ETV 1.0mg/dLAM | Median 38 (16–74)40 (17–70) | 9.48±1.819.24±1.56 | 123.9±109.72131.9±165.11 | P | No | 52 weeks | HBeAg seroconversion; HBeAg loss; ALT normalization; SAE |
| Chan HL 2007a[44] | 16 outpatient gastroenterology clinics at academic centers in 9 countries | NCT00115245 | Yes | LTDADF | Mean 34 (18-60)Mean 30 (19-47) | 9.57 ± 0.269.98± 0.23 | 183±23.6199 ±25.7 | P | Yes | 24 weeks | HBeAg seroconversion; HBeAg loss; ALT normalization;Undetectable HBV DNA |
| Chan HL 2007b[45] | 8 sites in China | — | Yes | LAMPlacebo | 39±1039±11 | 5.7±1.65.6±1.5 | △2.1±1.72.6±2.3 | N | Yes | 24 months | ALT normalization; Undetectable HBV DNA; SAE; HCC incidence |
| Yao GB 2007a[46] | 5 sites in China | — | Yes | ETV 1.0mg/dPlacebo | 34 (16-66)38 (19-57) | 8.84 ± 0.888.60 ± 0.80 | 85.04 ± 96.6104.24 ± 91.5 | B | No | 12 weeks | ALT normalization; Undetectable HBV DNA; SAE |
| Yao GB 2007b[47] | 26 sites in China | — | Yes | ETV 0.5mg/dLAM | 30±930±9 | 8.64±0.998.48 ±1.12 | 196 ±140198±180 | B | Yes | 48 weeks | HBeAg seroconversion; HBeAg loss; ALT normalization; Undetectable HBV DNA; SAE |
| Marcellin P 2008[48] | 106 clinical sites in 15 countries | NCT00116805; NCT00117676 | Yes | TDFADF | P 34±11, N 44±10.6;P 34±12, N 43±10.0 | P 8.64±1.076, N 6.86±1.31;P 8.88±0.930, 6.98±1.27 | P 142±102.81, N 127.5±101.21;P 155±121.49, N 163.6±146.02 | P for NCT00116805; N for NCT00117676 | Yes | 48 weeks | HBeAg seroconversion; ALT normalization; Undetectable HBV DNA; SAE |
| Leung N 2009[49] | 26 centers from eight countries | NCT00096785 | Yes | ETV 0.5mg/dADF | 37±2.432±2.0 | 10.26±0.309.88±0.22 | 110.6±14.6172.3±37.0 | P | Yes | 48 weeks | HBeAg seroconversion; HBeAg loss; ALT normalization; Undetectable HBV DNA; SAE |
| Liaw YF 2009[50] | 112 academic centers in 20 countries on 4 continents | NCT00057265 | Yes | LTDLAM | P 32 (16–63), N 43 (17–68);P 33 (16–67), N 43 (18–68) | P 9.5±0.09, N 7.7±0.12;P 9.5±0.09; N 7.4±0.10 | P 146.4±5.37, N 137.0±6.94;P 158.9±6.30, N 143.7±8.74 | B | Yes | 104 week | HBeAg seroconversion; HBeAg loss; ALT normalization; Undetectable HBV DNA; SAE |
| Shindo M 2009[51] | 38 institutions in Japan | — | Yes | ETV 0.5mg/dLAM | 39.8±10.442.3±12.6 | 8.39 ± 0.737.94 ± 0.83 | 142.4 ± 82.2185.0 ± 130.8 | B | Yes | 22 weeks | HBeAg seroconversion; HBeAg loss; ALT normalization; Undetectable HBV DNA; SAE |
| Lin Q 2010[52] | One hospital in Chong Qing, China | — | No | ETV 0.5mg/dADF | 35.00±7.2135.00±7.69 | 7.94±1.217.56±1.63 | 155.29±100.98155.74±86.28 | B | No | 48 weeks | HBeAg seroconversion; HBeAg loss; ALT normalization; Undetectable HBV DNA |
| Huang J 2011[53] | One hospital in Guang dong, China | — | No | LTDETV 0.5mg/d | 28.8±9.831.0±1.0 | 6.87±0.977.13±1.11 | 150.6±91.0163.1±105.7 | P | Yes | 52 weeks | HBeAg seroconversion; HBeAg loss; ALT normalization; Undetectable HBV DNA |
| Li D 2011[54] | One hospital in Hunan, China | — | No | ETV 0.5mg/dLAM | 45.71±6.544.82±7.21 | 8.52±0.418.41±0.39 | 171.84±130.21178.93±140.52 | B | Yes | 48 weeks | HBeAg seroconversion; ALT normalization; Undetectable HBV DNA |
| Pradeep KS 2011[55] | One hospital in New Delhi | — | No | ADFLAM | 29.73±10.0625.33±6.64 | Median 4.8×109±1.7×1010 IU/mlMedian 5.6×109±2.1×1010 IU/ml (copies/ml) | Median 84 (74-100)Median 85 (80-109) | B | Yes | 6 months | HBeAg seroconversion; Undetectable HBV DNA |
| Safadi R 2011[56] | 40 centers global trial | — | Yes | LTDLAM | 35.5±1.037.3±1.0 | 5.6±0.216.0±0.24 | 68.5±7.157.7±4.8 | B | Yes | 52 weeks | HBeAg seroconversion; HBeAg loss; ALT normalization; Undetectable HBV DNA; SAE |
| Heo J 2012[57] | 5 centers in Korea | NCT00625560 | Yes | LAMETV 1.0mg/d | 43 (24-91)43 (19-68) | 4.66±1.694.55±1.82 | 32.6±16.1(SE)37.1±35.5(SE) | P | No | 96 weeks | HBeAg seroconversion; HBeAg loss; Undetectable HBV DNA; HCC incidence |
| Ma XJ 2012[58] | One hospital in Guangdong, China | — | No | LAMADF | 41.6±18.942.6±22.8 | 6.7±1.37.0±1.3 | 105.2±89.4149.4±75.3 | B | Yes | 48 weeks▲ | HBeAg seroconversion; HBeAg loss; Undetectable HBV DNA |
| Jia JD 2014[59] | Multicenters in China | NCT00131742 | Yes | LTDLAM | P 28 (16-64), N 38 (20-56);P 29 (15-63), N 36 (19-58) | P 9.3 (0.123 SE), N 7.8 (0.389);P 9.7 (0.133), N 7.6 (0.346) | P 156 (9.6), N 162 (23.9);P 157 (12.6), N 177 (75.2) | B | Yes | 104 weeks | HBeAg seroconversion; HBeAg loss; ALT normalization; Undetectable HBV DNA; SAE |
| Hou JL 2015[60] | 22 sites in China | NCT01300234 | Yes | TDFADF | 36.1 (18–66)36.4 (18–66) | P 8.7±0.87;N 6.9±1.18P 8.7±0.79;N 7.0±1.13 | P 199.1±132.8;N 133.4±120.9;P 189.0±121.5; N112.6±80.3 | B | Yes | 48 weeks | HBeAg seroconversion; HBeAg loss; ALT normalization; Undetectable HBV DNA; SAE |
| Su M 2015[61] | One hospital in Zhejiang, China | — | No | ADFETV 0.5mg/d | 36.12±8.6134.89±7.34 | 6.61±0.946.64±0.86 | — | P | No | 12 months | HBeAg loss; ALT normalization; Undetectable HBV DNA |
| Ahn HS 2016[62] | Six hospital clinics in South Korea | NCT00625339 | Yes | ETV 0.5mg/dLAM | Median 41.5 (18–59)44.2 (25–62) | 4.6±1.84.7±1.7 | 23.5±12.325.6±13.4 | P | Yes | 96 weeks | HBeAg seroconversion; HBeAg loss; ALT normalization; Undetectable HBV DNA; HCC incidence |
| Lin HX 2016[63] | One hospital in Fujian, China | — | No | TDFETV 0.5mg/d | 32.4±7.833.6±10.3 | 7.5±0.96.7±1.4 | 165.9±124.5176.6 ± 132.9 | P | Yes | 96 weeks | HBeAg seroconversion; HBeAg loss; Undetectable HBV DNA |
| Luo XD 2016[64] | One hospital in Guangdong, China | — | No | LTDETV 0.5mg/d | 28.81±0.7729.08±1.07 | 5.985±0.1266.047±0.140 | 73.06±12.3856.29±6.91 | P | No | 208 weeks | HBeAg seroconversion; HBeAg loss; Undetectable HBV DNA |
| Yang W 2016[65] | One hospital in Shandong, China | — | No | LTDETV 0.5mg/d | 34.25±6.3933.76±7.21 | 6.82±1.347.46±1.93 | 160.54±93.21165.57±86.44 | P | Yes | 48 weeks | HBeAg seroconversion; Undetectable HBV DNA |
| An J 2017[66] | One medical center in South Korea | NCT01595685 | No | LTDETV 0.5mg/d | 48±1147±10 | — | Median 24 (16–31)19 (14–27) | B | No | 48 weeks | HBeAg seroconversion; HBeAg loss; SAEHCC incidence |
| Sriprayoon T 2017[67] | One hospital in Thailand | — | Yes | ETV 0.5mg/dTDF | 41.6 ± 11.541.2 ± 11.6 | P7.1 ± 1.5, N4.9 ± 1.3;P 7.0 ± 1.4, N 5.0 ± 1.3 | 68.1 ± 64.176.8 ± 79.8 | B | Yes | 144 weeks | HBeAg seroconversion; HBeAg loss; ALT normalizationUndetectable HBV DNA; HCC incidence |
| Zhang DF 2017[68] | One hospital in Tianjin, China | — | No | TDFETV 0.5mg/d | 35.9±10.636.1±9.8 | 6.56±0.666.73±0.81 | 135.3±33.4130.5±31.9 | B | Yes | 48weeks | HBeAg seroconversion |
| Koike K 2018[69] | Participants from 32 hospitals in Japan | NCT01480284/GSK LOC115409 | Yes | TDFETV 0.5mg/d | 45.4±9.2346.1±9.68 | 7.00±1.4987.19±1.313 | 90.4±99.1376.7±80.70 | B | Yes | 48weeks | HBeAg seroconversion; ALT normalization |

*ADF: adefovir dipivoxil; ETV: entecavir, LAM: lamivudine; LTD: telbivudine; TDF: tenofovir disoproxil fumarate; PLA: placebo;*

*HBV DNA: hepatitis B virus (HBV) deoxyribonucleic acid (DNA); ALT: alanine aminotransferase; HCC: hepatocellular carcinoma;*

*P: Positive; N: Negative; B: Both;*

*For baseline data, mean and standard deviation were used if not stated (age, HBV DNA, ALT);*

*Duration of treatment: only for the randomized phase;*

*AAA: ADV in the first randomized phase, then ADV in the second phase; AAP: ADV in the first randomized phase, then placebo in the second phase; PAA: placebo in the first randomized phase, then ADV in the second phase;*

*\*For both groups; △Alanine aminotransferase — no. of times the upper limit of the normal range; ▲Only the randomized period was included in the network meta-analysis.*

**Appendix 5. Risk of bias of included studies**

Supplementary Table 2. Risk of bias of the included studies

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| ID | Random sequence generation | Allocation concealment | Blinding of participants/personnel | Incomplete outcome data | Other bias▲ |
| Judgment | Quota | Judgment | Quota | Judgment | Quota | Judgment | Quota | Other consideration | Judgment |
| Marcellin P 2003[34] | Low | The central randomization scheme was stratified according to geographic regions. | Low | The central randomization scheme was stratified according to geographic regions. | Low | The placebo and ADF were formulated to be indistinguishable from one another in appearance and taste. | Low | I ADF 10mg 1/172, C 3/170 (took No medication) | mITT analysis | High |
| Schiff ER 2003[35] | Low | Computer-generated allocation scheme | Low | The randomization envelope was used. | Low | Treatment assignments in LAM and PLA remained blinded until end-of-study.  | Low | I 9/119; C 10/56 | mITT analysis | High |
| Yao GB 2003[36] | Unclear | 　 | Unclear | 　 | Low | Double-blind, double dummy | Low | Not mentioned | mITT analysis | High |
| Peters MG 2004[37] | Low | Patients were randomized centrally. | Low | Patients were randomized centrally. | Low | Patients and investigators were blinded.  | Low | I 1/20; C 1/20(discontinued the study before receiving any treatment) | mITT analysis | High |
| Chang TT 2005[38] | Low | Randomization was performed using a centralized interactive voice randomization system and was stratified by site. | Low | Randomization was performed using a centralized interactive voice randomization system and was stratified by site. | Low | Blinded therapy | Low | Not mentioned | mITT analysis | High |
| Lai CL 2005[39] | Low | Randomized via a central randomization scheme using an interactive voice response system. | Low | Randomized via a central randomization scheme using an interactive voice response system. | Low | The system linked to the study drug supply vendor for dispensing of blinded study medications to the study sites. Treatment assignments remained double blinded for the duration of the study. | Low | 3/107\* (Three patients withdrew before baseline (first day of treatment)) | mITT analysis | High |
| Zeng MD 2005[40] | Low | Central telephone randomization system | Low | Central telephone randomization system | Unclear |  | Low | 2/480 | mITT analysis | High |
| Chang TT 2006[41] | Low | Treatment assignments were allocated centrally on the basis of permuted block sizes of four that were assigned within each center. | Low | Treatment assignments were allocated centrally on the basis of permuted block sizes of four that were assigned within each center. | Low | Double-blind, double dummy trial | Low | I 14/354; C 34/355 | mITT analysis | High |
| Lai CL 2006[42] | Low | Treatment assignments were allocated centrally on the basis of permuted block sizes of four that were assigned within each center. | Low | Treatment assignments were allocated centrally on the basis of permuted block sizes of four that were assigned within each center. | Low | Double-blind, double dummy trial | Low | I 6/331; C 4/317 | mITT analysis | High |
| Sherman M 2006[43] | Low | Patients were randomized centrally using an interactive voice response system. Randomization was accomplished using blocks of permuted treatment assignments and was stratified by study site. | Low | Patients were randomized centrally using an interactive voice response system. Randomization was accomplished using blocks of permuted treatment assignments and was stratified by study site. | Low | Double-blind, double dummy trial. Investigators, patients, and study sponsor were blinded to results and treatment assignment. | Low | I 14/147 (6 patients no longer met inclusion criteria before treatment); C 20/146 (1 patient withdrew consent before treatment) | mITT analysis  | High |
| Chan HL 2007a[44] | Low | A centralized computer-generated process assigned eligible patients to each of the treatment groups by using block randomization, implemented with an automated voice-response system. | Low | A centralized computer-generated process assigned eligible patients to each of the treatment groups by using block randomization, implemented with an automated voice-response system. | Low | The brittle nature of ADF tablets precluded treatment blinding by routine over-encapsulation. Investigators were blinded to HBV serologic data from baseline until week 52. Blinding was unlikely broken. | Low | I 2/45 (1 pregnancy); C 3/91 (1 patient withdrew consent, 1 non-adherence) | mITT analysis | High |
| Chan HL 2007b[45] | Low | Randomization was centralized and stratified according to the geographical regions. | Low | Randomization was centralized and stratified according to the geographical regions. | Low | Double-blind, patients received lamivudine or matching placebo. | High | month 24: I 19/89; C 12/47 | Although mITT analysis, losses of follow-up were high in the comparison group | High |
| Yao GB 2007a[46] | Unclear | 　 | Unclear | 　 | Low | Mean exposure to ETV during the double-blind dosing phase was 12 weeks (blinded treatment). | Low | I 0/116; C 1/29 | mITT analysis | High |
| Yao GB 2007b[47] | Low | Randomization was performed centrally and stratified by HBeAg status and investigative site. | Low | Randomization was performed centrally and stratified by HBeAg status and investigative site. | Low | Double-blind, double-dummy  | Low | I 10/258; C 16/261 | mITT analysis | High |
| Marcellin P 2008[48] | Low | With the use of a central, interactive voice-response system . | Low | With the use of a central, interactive voice-response system. | Low | Masking: Quadruple (participant, care provider, investigator, outcomes assessor) | Low | I 16/426; C 9/215 | mITT analysis | High |
| Leung N 2009[49] | Unclear | 　 | Unclear | 　 | High | Open-label | High | I 3/36; C 1/34 (discontinued therapy before week 12) | Per-protocol analysis for efficacy, mITT analysis for safety | High |
| Liaw YF 2009[50] | Low | Randomly assigned in block sizes of four; randomized using a computer-generated code via central telephone | Low | Randomly assigned in block sizes of four; randomized using a computer-generated code via central telephone | Low | Double-blind, double dummy | Low | I 59/683\*; C 88/687 (withdrew before week 104) \*3 did not return after randomization | mITT analysis | High |
| Shindo M 2009[51] | Low | Patients were stratified according to HBeAg status and study site  | Unclear | 　 | Low | Double-blind, double-dummy study | Low | I 0.5mg 2/34; C 1/34 | mITT analysis | High |
| Lin Q 2010[52] | Unclear | 　 | Unclear | 　 | Unclear |  | Low | No losses to follow up | mITT analysis | Low |
| Huang J 2011[53] | Unclear | 　 | Unclear | 　 | High | Open-label | Low | No losses to follow up | mITT analysis | Low |
| Li D 2011[54] | Unclear | 　 | Unclear | 　 | Unclear | 　 | Low | Not mentioned | mITT analysis | Low |
| Pradeep KS 2011[55] | Unclear | 　 | Unclear | 　 | Unclear |  | Low | Not mentioned | mITT analysis | Low |
| Safadi R 2011[56] | Low | Randomized by an IVRS system | Low | Randomized by an IVRS system  | Unclear |  | Low | I 6/122; C 8/124 | mITT analysis | High |
| Heo J 2012[57] | Low | Patients were randomized and allocated to treatment by a central investigator using a computer-generated number pre-assigned to a treatment arm. | Low | Patients were randomized and allocated to treatment by a central investigator using a computer-generated number pre-assigned to a treatment arm. | High | Open-label | High | I 25/36 (1 consent withdrawn; 24 emergence of resistance); C 2/36 (2 consent withdrawn) | mITT analysis | High |
| Ma XJ 2012[58] | Low | Randomized sequence was made by computer. | Unclear | 　 | High | Open-label | Low | No losses of follow-up | mITT analysis | Low |
| Jia JD 2014[59] | Low | A centralized telecommunication-based interactive voice response system was used for patient randomization. | Low | A centralized telecommunication-based interactive voice response system was used for patient randomization. | Low | Double-blind, double-dummy | Low | I 11/167; C 21/165 | mITT analysis　 | High |
| Hou JL 2015[60] | Low | Randomization schedule generated by a validated GlaxoSmithKline system (RANDALL). | Low | Randomization schedule generated by a validated GlaxoSmithKline system (RANDALL). | Low | Masking: Double (participant, investigator); Placebo tablets were visually identical to the corresponding active study medication. | Low | I 4/257; C 10/255 (3 were randomized but not dosed) | mITT | High |
| Su M 2015[61] | Low | Coin tossing | Unclear | 　 | Unclear | 　 | Low | Not mentioned | mITT analysis | Low |
| Ahn HS 2016[62] | Low | Randomized treatment and allocation were carried out by a central investigator using a computer-generated number pre-assigned to a treatment arm. | Low | Randomized treatment and allocation were carried out by a central investigator using a computer-generated number pre-assigned to a treatment arm. | High | Open-label | Low | I 1/38; C 8/35 | mITT analysis | High |
| Lin HX 2016[63] | Unclear | 　 | Unclear | 　 | Unclear | 　 | Low | Not mentioned | mITT analysis | Low |
| Luo XD 2016[64] | Unclear | 　 | Unclear | 　 | Unclear | 　 | Low | LTD 6/95; ETV4/ 93 | mITT analysis | Low |
| Yang W 2016[65] | Unclear | 　 | Unclear | 　 | Unclear | 　 | Low | Not mentioned | mITT analysis | Low |
| An J 2017[66] | Low | The patients were randomized ratio using a centralized procedure and an interactive web response system. | Low | The patients were randomized ratio using a centralized procedure and an interactive web response system. | High | Open-label | High | I 17/47; C 1/50 | mITT analysis (Patients who discontinued the study prior to week 48 were considered failures for all endpoints from the time of discontinuation) | Low |
| Sriprayoon T 2017[67] | Unclear | 　 | Unclear | 　 | Unclear | 　 | Low | I 5/205; C 6/206 (5 in ETV group, 6 in TDF group became pregnant) | mITT analysis | High |
| Zhang DF 2017[68] | Low | Computer generated random sequence | Unclear |  | Low | Single-blinded (patients): TDF and ETV were provided in identical formats in terms of shape, size, texture and packing | Low | TDF 8/98; ETV 10/98 | ITT analysis | Low |
| Koike K 2018[69] | Unclear |  | Unclear |  | Low | Double-blinded study | Low | I 1/110 (1 withdrew consent); C 0/56 | mITT analysis | High |

*\* Three patients withdrew before baseline (first day of treatment).*

*△mITT: modified intention-to-treat, the intent-to-treat population comprised all randomized patients who received at least one dose of study medication.*

*▲academic bias and funding bias*

*I: intervention group; C: comparison group*

*ADF: adefovir dipivoxil; ETV: entecavir, LAM: lamivudine; LTD: telbivudine; TDF: tenofovir disoproxil fumarate; PLA: placebo*

**Appendix 6. Forest plots for direct comparisons**



Supplementary Figure 2. Forest plot for HBeAg seroconversion



Supplementary Figure 3. Forest plot for HBeAg loss



Supplementary Figure 4. Forest plot for ALT normalization



Supplementary Figure 5. Forest plot for achieving undetectable HBV DNA



Supplementary Figure 6. Forest plot for serious adverse events

**Appendix 7.** **Network plots**



Supplementary Figure 7. Network plot of the comparisons for HBeAg seroconversion



Supplementary Figure 8. Network plot of the comparisons for HBeAg loss



Supplementary Figure 9. Network plot of the comparisons for ALT normalization



Supplementary Figure 10. Network plot of the comparisons for achieving undetectable HBV DNA

**

Supplementary Figure 11. Network plot of the comparisons for serious adverse events

**Appendix 8. Rank probabilities and SUCRA plots**



Supplemental Figure 12. Rank probabilities for HBeAg seroconversion

Rankograms shows probability of each treatment strategy to become the best choice for HBeAg seroconversion.



Supplementary Figure 13. SUCRA for HBeAg seroconversion

SUCRA plot shows probability of each strategy having each specific rank (1–6) for HBeAg seroconversion. Ranking indicates the probability to be the best treatment, the second best, the third best and so on.



Supplementary Figure 14. Rank probabilities for HBeAg loss



Supplementary Figure 15. SUCRA for HBeAg loss

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Supplementary Figure 16. Rank probabilities for ALT normalization



Supplementary Figure 17. SUCRA for ALT normalization



Supplementary Figure 18. Rank probabilities for achieving undetectable HBV DNA



Supplementary Figure 19. SUCRA for achieving undetectable HBV DNA

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Supplementary Figure 20. Rank probabilities for serious adverse events



Supplementary Figure 21. SUCRA for serious adverse events

**Appendix 9. Iterative trajectory for WinBUGS models**



Supplementary Figure 22. Iterative trajectory for HBeAg seroconversion.

The trajectory became stable and the model converged.



Supplementary Figure 23. Iterative trajectory for HBeAg loss.

The trajectory became stable and the model converged.



Supplementary Figure 24. Iterative trajectory for ALT normalization.

The trajectory became stable and the model converged.



Supplementary Figure 25. Iterative trajectory for undetectable HBV DNA.

The trajectory became stable and the model converged.



Supplementary Figure 26. Iterative trajectory for serious adverse events.

The trajectory became stable and the model converged.

**Appendix 10. Incidence of hepatocellular carcinoma**

Supplementary Table 3. Incidence of hepatocellular carcinoma (Pooled RR, 95%CI)

|  |  |  |
| --- | --- | --- |
| Intervention vs Comparator | Direct comparison | Indirect comparison |
| Lamivudine vs Placebo | 1.58 (0.17,14.81) | — |
| Entecavir vs Lamivudine | 0.54 (0.12,2.53) | — |
| Entecavir vs Telbivudine | 0.44 (0.02,10.59) | — |
| Entecavir vs Tenofovir | 4.00 (0.45,35.47) | — |
| Entecavir vs Placebo | — | 0.86 (0.06,12.98) |
| Telbivudine vs Tenofovir | — | 9.01 (0.19,419.98) |

**Appendix 11. GRADE summary of findings table**

Supplementary Table 4. Summary of findings for HBeAg seroconversion: direct comparisons

|  |
| --- |
| Question: Should nucleos(t)ide analogues be used for treating chronic hepatitis B virus infection?Bibliography: Nucleos(t)ide analogues for the treatment of chronic hepatitis B virus infection |
| **Quality assessment** | **Summary of Findings** |
| **Participants(studies)Follow up** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Publication bias** | **Overall quality of evidence** | **Study event rates (%)** | **Relative effect**(95% CI) | **Anticipated absolute effects** |
| **With** | **With Nucleos(t)ide analogues** | **Risk with** | **Risk difference with Nucleos(t)ide analogues**(95% CI) |
| **HBeAg seroconversion** (CRITICAL OUTCOME; assessed with: ADF vs PLA) |
| 798(2 studies) | serious1 | serious2 | no serious indirectness | no serious imprecision | reporting bias strongly suspected 3 | ⊕⊕⊝⊝**LOW**1,2,3,4due to risk of bias, inconsistency, publication bias, large effect | 10/283 (3.5%) | 35/515 (6.8%) | **RR 2.43**(1.2 to 4.94) | **Study population** |
| **35 per 1000** | **51 more per 1000**(from 7 more to 139 more) |
| **Moderate** |
| **31 per 1000** | **44 more per 1000**(from 6 more to 122 more) |
| **HBeAg seroconversion** (CRITICAL OUTCOME; assessed with: LAM vs PLA) |
| 161(1 study) | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | reporting bias strongly suspected 3 | ⊕⊕⊕⊝**MODERATE**3due to publication bias | 7/53 (13.2%) | 19/108 (17.6%) | **RR 1.33**(0.6 to 2.97) | **Study population** |
| **132 per 1000** | **44 more per 1000**(from 53 fewer to 260 more) |
| **Moderate** |
| **132 per 1000** | **44 more per 1000**(from 53 fewer to 260 more) |
| **HBeAg seroconversion** (CRITICAL OUTCOME; assessed with: ADF vs TDF) |
| 435(2 studies) | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | reporting bias strongly suspected 3 | ⊕⊕⊕⊝**MODERATE**3due to publication bias | 48/256 (18.8%) | 23/179 (12.8%) | **RR 0.74**(0.47 to 1.16) | **Study population** |
| **188 per 1000** | **49 fewer per 1000**(from 99 fewer to 30 more) |
| **Moderate** |
| **182 per 1000** | **47 fewer per 1000**(from 96 fewer to 29 more) |
| **HBeAg seroconversion** (CRITICAL OUTCOME; assessed with: ETV vs TDF) |
| 484(4 studies) | very serious5 | no serious inconsistency | no serious indirectness | no serious imprecision | reporting bias strongly suspected 3 | ⊕⊝⊝⊝**VERY LOW**3,5due to risk of bias, publication bias | 51/240 (21.3%) | 47/244 (19.3%) | **RR 0.84**(0.6 to 1.19) | **Study population** |
| **212 per 1000** | **34 fewer per 1000**(from 85 fewer to 40 more) |
| **Moderate** |
| **169 per 1000** | **27 fewer per 1000**(from 68 fewer to 32 more) |
| **HBeAg seroconversion** (CRITICAL OUTCOME; assessed with: ADF vs LTD) |
| 133(1 study) | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | reporting bias strongly suspected 3 | ⊕⊕⊕⊝**MODERATE**3due to publication bias | 7/44 (15.9%) | 9/89 (10.1%) | **RR 0.64**(0.25 to 1.59) | **Study population** |
| **159 per 1000** | **57 fewer per 1000**(from 119 fewer to 94 more) |
| **Moderate** |
| **159 per 1000** | **57 fewer per 1000**(from 119 fewer to 94 more) |
| **HBeAg seroconversion** (CRITICAL OUTCOME; assessed with: ETV vs LTD) |
| 517(4 studies) | very serious6 | serious2 | no serious indirectness | no serious imprecision | undetected | ⊕⊝⊝⊝**VERY LOW**2,6due to risk of bias, inconsistency | 96/263 (36.5%) | 56/254 (22%) | **RR 0.59**(0.45 to 0.78) | **Study population** |
| **365 per 1000** | **150 fewer per 1000**(from 80 fewer to 201 fewer) |
| **Moderate** |
| **297 per 1000** | **122 fewer per 1000**(from 65 fewer to 163 fewer) |
| **HBeAg seroconversion** (CRITICAL OUTCOME; assessed with: LAM vs LTD) |
| 1359(3 studies) | serious1 | no serious inconsistency | no serious indirectness | no serious imprecision | reporting bias strongly suspected 3 | ⊕⊕⊝⊝**LOW**1,3due to risk of bias, publication bias | 188/677 (27.8%) | 150/682 (22%) | **RR 0.79**(0.66 to 0.96) | **Study population** |
| **278 per 1000** | **58 fewer per 1000**(from 11 fewer to 94 fewer) |
| **Moderate** |
| **290 per 1000** | **61 fewer per 1000**(from 12 fewer to 99 fewer) |
| **HBeAg seroconversion** (CRITICAL OUTCOME; assessed with: ADF vs LAM) |
| 130(3 studies) | very serious7 | no serious inconsistency | no serious indirectness | no serious imprecision | reporting bias strongly suspected 3 | ⊕⊝⊝⊝**VERY LOW**3,7due to risk of bias, publication bias | 16/73 (21.9%) | 17/57 (29.8%) | **RR 1.55**(0.93 to 2.59) | **Study population** |
| **219 per 1000** | **121 more per 1000**(from 15 fewer to 348 more) |
| **Moderate** |
| **67 per 1000** | **37 more per 1000**(from 5 fewer to 107 more) |
| **HBeAg seroconversion** (CRITICAL OUTCOME; assessed with: ETV vs LAM) |
| 1778(8 studies) | very serious8 | no serious inconsistency | no serious indirectness | no serious imprecision | reporting bias strongly suspected 3 | ⊕⊝⊝⊝**VERY LOW**3,8due to risk of bias, publication bias | 123/877 (14%) | 141/901 (15.6%) | **RR 1.12**(0.9 to 1.4) | **Study population** |
| **140 per 1000** | **17 more per 1000**(from 14 fewer to 56 more) |
| **Moderate** |
| **103 per 1000** | **12 more per 1000**(from 10 fewer to 41 more) |
| **HBeAg seroconversion** (CRITICAL OUTCOME; assessed with: ADF vs ETV) |
| 149(2 studies) | very serious7 | serious2 | no serious indirectness2 | no serious imprecision | reporting bias strongly suspected 3 | ⊕⊝⊝⊝**VERY LOW**2,3,7due to risk of bias, inconsistency, publication bias | 18/75 (24%) | 12/74 (16.2%) | **RR 0.73**(0.18 to 2.97) | **Study population** |
| **240 per 1000** | **65 fewer per 1000**(from 197 fewer to 473 more) |
| **Moderate** |
| **236 per 1000** | **64 fewer per 1000**(from 194 fewer to 465 more) |

1 Performance bias was unclear for one included study.
2 The directions of individual results for all included studies were not the same.
3 Funding/support/funding or financial support from pharmaceutical companies; several authors worked for pharmaceutical companies
4 2<RR<5
5 Selection bias for three included studies were unknown, and the blinding method was not mentioned in two included studies.
6 Selection bias of three included studies were unclear, high risk of performance bias was detected in two of the included studies.
7 Selection bias was unclear for two included studies, and blinding was not used for one included study which might lead to performance bias.
8 Selection bias was unclear for two included studies, and blinding was not used in two included studies which might lead to performance bias

Supplementary Table 5. Summary of findings for HBeAg seroconversion: direct, indirect and network comparisons

|  |  |  |  |
| --- | --- | --- | --- |
| Intervention | Direct | Indirect | NetWork |
| RR(95%CI) | Quality | RR(95%CI) | Quality | RR(95%CI) | Quality |
| ADF vs PLA  | **2.43 (1.20,4.94)** | Low | 2.06(0.80,5.33) | Moderate | **2.40(1.27,4.25)** | Moderate |
| ETV vs PLA | - | - | 1.49(0.65,3.42) | Low | **2.40(1.20,4.46)** |  Low |
| LAM vs PLA | 1.33 (0.60,2.97) | Moderate | 1.57(0.66,3.76) | Very low | **2.21(1.11,4.07)** | Moderate |
| LTD vs PLA | - | - | 1.68(0.74,3.83) | Low | **3.60(1.76,6.70)** | Low |
| TDF vs PLA | - | - | **3.28(1.42,7.60)** | Low | **2.78(1.26,5.42)** | Low |
| ADF vs TDF  | 0.74 (0.47,1.16) | Moderate | 0.61(0.15,2.60) | Very low | 0.91(0.55,1.44) | Moderate |
| ETV vs TDF | 0.84 (0.60,1.19) | Very low | 1.01(0.23,4.42) | Moderate | 0.90(0.57,1.36) | Moderate |
| LAM vs TDF | - | - | 0.75(0.50,1.13) | Very low | 0.83(0.50,1.30) | Very low |
| LTD vs TDF | - | - | 1.62(0.80,3.25) | Very low | 1.35(0.81,2.13) | Very low |
| ADF vs LTD  | 0.64 (0.25,1.59) | Moderate | 0.38(0.08,1.75) | Very low | 0.69(0.43,1.06) | Moderate |
| ETV vs LTD | **0.59 (0.45,0.78)** | Very low | 0.89(0.66,1.18) | Low | **0.67(0.52,0.86)** | Low |
| LAM vs LTD | **0.79 (0.66,0.96)** | Low | **0.46(0.24,0.89)** | Very low | **0.62(0.50,0.76)** | Low |
| ADF vs LAM | 1.55 (0.93,2.59) | Very low | 1.53(0.73,3.22) | Very low | 1.12(0.71,1.68) | Very low |
| ETV vs LAM | 1.12 (0.90,1.40) | Very low | 1.13(0.47,2.71) | Very low | 1.09(0.87,1.25) | Very low |
| ADF vs ETV | 0.73 (0.18,2.97) | Very low | 0.72(0.41,1.26) | Very low | 1.03(0.66,1.54) | Very low |