Table 1. Level of evidence based on the Oxford Centre for Evidence-based Medicine.

Level	Criteria	Simple model for high, intermediate and low evidence
1	Systematic reviews (SR) (with homogeneity) of randomised-controlled trials (RCT)	Further research is unlikely to change our confidence in the estimate of benefit and risk
2	RCT or observational studies with dramatic effects; SR of lower quality studies (*i.e.* non-randomised, retrospective)	
3	Non-randomised-controlled cohort/follow-up study/control arm of randomised trial (systematic review is generally better than an individual study)	Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate
4	Case-series, case-control, or historically controlled studies (systematic review is generally better than an individual study)	
5	Expert opinion (mechanism-based reasoning)	Any estimate of effect is uncertain

Table 2. Grades of recommendation.

Grade	Wording	Criteria
Strong	Shall, should, is recommended. Shall not, should not, is not recommended.	Evidence, consistency of studies, risk-benefit ratio, patient preferences, ethical obligations, feasibility
Weak or open	Can, may, is suggested. May not, is not suggested.	

safety in randomised trials conducted mostly in patients without cirrhosis.[17,18] All but two systematic reviews and a meta-analysis showed a significantly lower risk of HCC or a trend towards lower risk in patients receiving tenofovir.[19–22] However, all studies included a limited number of patients with cirrhosis and showed high heterogeneity. In one study a trend towards lower risk of HCC was observed in patients with cirrhosis (adjusted hazard ratio [HR] 0.87, 95% CI 0.74–1.01) and not in patients without cirrhosis (adjusted HR 1.14, 95% CI 0.81–1.60).[23] An individual patient meta-analysis which included 42,939 patients (6,979 receiving tenofovir and 35,960 receiving entecavir) concluded that tenofovir was not associated with a lower risk of HCC compared with entecavir (HR 0.81, 95% CI 0.65-1.01).[24] Regarding HCC recurrence, a recent meta-analysis concluded that tenofovir reduces the risk of late recurrence compared to entecavir (adjusted HR 0.58, 95% CI 0.45–0.76, p = 0.0%) but not early recurrence (adjusted HR 0.88, 95% CI 0.76–1.02, p = 34.8%).[25]

Hepatitis C

No RCTs have evaluated the impact of direct-acting antivirals (DAAs) on HCC development, *de novo* or recurrent, in patients with chronic hepatitis C virus (HCV) infection. DAAs are recommended to reduce the risk of developing cirrhosis or cirrhosis complications. Several cohort studies (retrospective and prospective) or systematic reviews and aggregated meta-analyses have assessed the risk of HCC development after DAA treatment.[26–30] However, only one individual data meta-

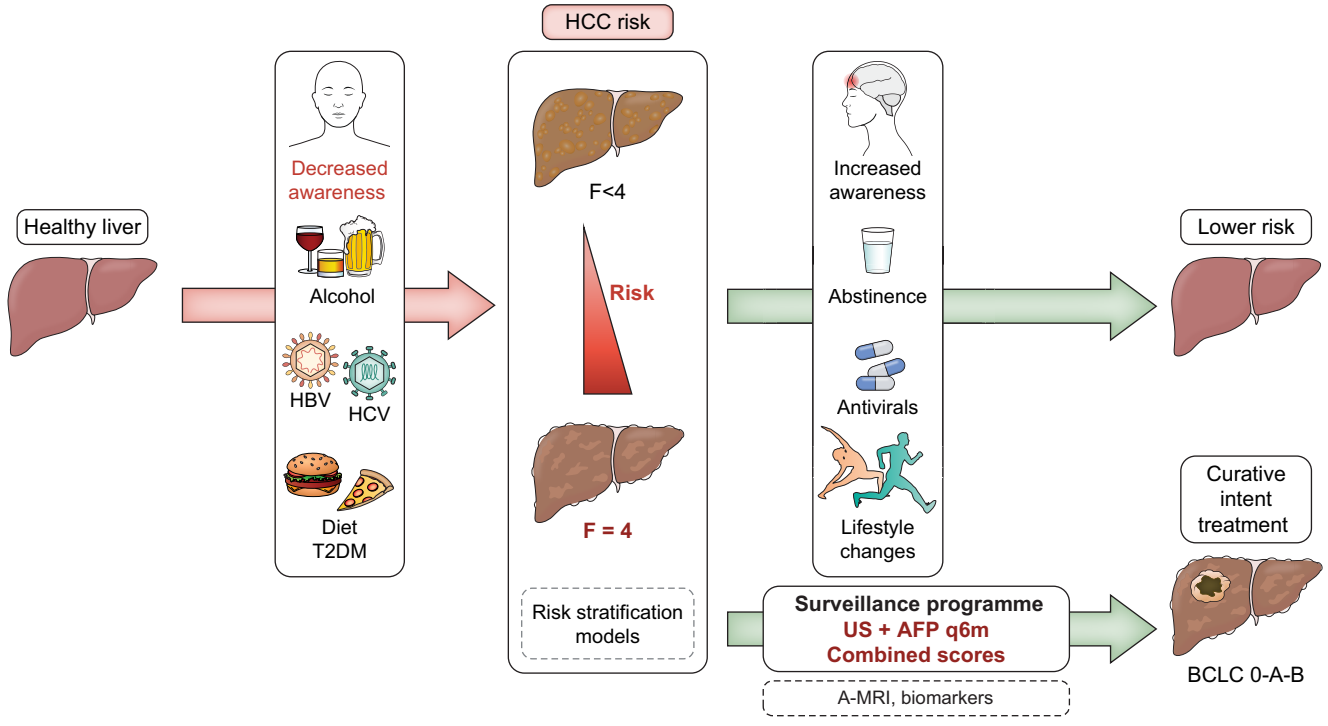

Fig. 1. Opportunities for the prevention of premature death related to HCC. AFP, alpha-fetoprotein; A-MRI, abbreviated magnetic resonance imaging; BCLC, Barcelona Clinic Liver Cancer; F, fibrosis; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; q6m, every six months; T2DM, type 2 diabetes mellitus; US, ultrasound. Dotted line boxes represent areas of ongoing research.