Monitoring for treatment response among people with CHB receiving treatment or not yet receiving treatment

- **Monitoring for people receiving treatment**
- For people **receiving treatment**, the following are recommended to be monitored at **least annually**:
- • **non-invasive tests** (**APRI score** or **transient elastography**) to assess stage of disease and progression of fibrosis or cirrhosis; and
- • **ALT level**(and AST for APRI), **HBV DNA levels** (when HBV DNA testing is available), **HBsAg** and **HBeAg/anti-HBe**
- • **Treatment adherence** should be monitored regularly and at **each visit**.

- **Monitoring for people not yet receiving treatment**
- People who **do not currently meet** the **criteria** for **antiviral therapy** (**persistently normal serum aminotransferase results and HBV DNA levels below 2000 IU/mL** (when HBV DNA testing is available) or
- who have expressed a desire to **defer treatment** may be monitored **annually** for disease progression and **ALT** and **HBV DNA** levels (when HBV DNA testing is available).(conditional recommendation, low-certainty evidence)

- **Among people receiving treatment**
- The **aim** of monitoring people **receiving treatment** is to **evaluate** the **effectiveness of treatment response, treatment adherence, adverse effects of treatment, progression of liver disease and development of HCC.**
- If **antiviral therapy is discontinued, liver function** should be **monitored closely**, since **severe acute exacerbations** of **hepatitis** have been reported, and **antiviral therapy** may **need** to be **resumed**.

- **Fluctuating** or **persistently abnormal serum ALT** and **HBV DNA levels >2000 IU/mL** can **indicate progressive disease** and the **need** for **treatment**.
- Conversely, **spontaneous improvement** may occur with a **decline** in **HBV replication,** with **normalization** of **ALT levels** and **seroconversion from HBeAg-positive** to **anti-HBe**.

- **Monitoring on antiviral therapy**
- **•The evidence from the previous 2015 review suggests that about 80% of HBeAg-positive people (and 50–70% of HBeAg-negative people) achieved treatment response (both undetectable levels of HBV DNA and normalized ALT levels) with potent nucleoside analogues (ETV and TDF) by week 48 of treatment, even people with decompensated cirrhosis**

- **Monitoring among those who do not meet treatment criteria**
- •Studies to investigate the monitoring of **ALT levels** among those who have **HBeAg-negative CHB** (formerly known as “**inactive carriers**”) to predict future ALT flares or elevation suggest that a minimum period of monitoring of **three months** would identify about 90% of people with flares.

- **Monitoring after antiviral therapy ends**
- A rise in **HBV DNA** typically **precedes** the **increase** in **ALT**, in this setting, and a **rise** to **10 000** to **100 000** IU/mL would **prompt rapid reinstitution of nucleoside analogue therapy** to **avoid** a **severe flare**. **People who stop TDF therapy may experience a rise in serum aminotransferases earlier than those who stop ETV.**

- **monitoring HBeAg** may be **helpful** in **some situations** (**indicating** the **presence** of **active HBV replication** and **high infectivity**, and **spontaneous improvement** may occur **following HBeAg** to **anti-HBe seroconversion** in association with a **decline** in **HBV replication** and **normalization** of **ALT levels**, which confers a **good prognosis**).

- **Data** from **multiple clinical trials** show that **potent nucleoside analogues** (TDF, ETV and TAF) **suppress HBV DNA replication** to **low** or **undetectable levels** for **most people** by **24–48 weeks** of **treatment**, with **low rates** of **resistance** (**but** with **limited success** in **achieving loss of HBeAg for HBeAg-positive people or loss of HBsAg**).

- •**Monitoring after stopping antiviral therapy**
- **ALT** and **HBV DNA** can be **measured monthly** for **the first three months** and then **every three months** during the **first year** to detect severe exacerbations.

- **Retreatment** is **recommended** if there are consistent signs of **reactivation** (**HBsAg** or **HBeAg becomes positive**, **ALT levels increase** or **HBV DNA** becomes **detectable again**).
- **Biochemical relapse** has been variously defined but **includes** an **ALT elevation to >2 times the ULN.**

- A **hepatitis flare** has been defined as an **ALT elevation >5 times** the **ULN**, and **severe hepatitis flare** has been defined as **ALT level >1000** U/L or **ALT <1000 U/L plus** a **total bilirubin ≥3.5 mg/dL** or an **international normalized ratio ≥1.5**.
- **Viral relapse** has been defined as **HBV DNA >2000 IU/mL.**

- **Monitoring the safety of nucleoside analogues**
- •Recommendations
- •Existing and maintained recommendations from the 2015 hepatitis Bguidelines
- •**Before initiating antviral therapy**, people's baseline risk for **renal dysfunctiona** may be assessed and baseline renal functionb measured.
- •People receiving long-term **tenofovir** disoproxil fumarate therapy may be monitored **annually** for **renal function** and **children's growth** monitored carefully.(conditional recommendation, very-low-certainty evidence

Table 17.1 Recommended dosage for adults with renal impairment and decompensated cirrhosis and recommended dose reduction or dosing interval

Drug	CrCl (mL/min)[a]			
	>50	30–49	10–29	<10 Haemodialysis or continuous ambulatory peritoneal dialysis
TDF[b,c]	One 300-mg tablet every 24 hours (7.5 scoops of	One 300-mg tablet every 48 hours (or 160 mg [3 scoops] of powder every 24 hours)	One 300-mg tablet every 72–96 hours (or 60 mg [1.5 scoops] of powder every 24 hours)	Every seven days or one 300-mg tablet following completion of approximately every 12 hours of dialysis (or 20 mg [0.5 scoops] of powder following completion of approximately every 12 hours of dialysis)
ETV[d]	0.5 mg once daily	0.25 mg once daily **OR** 0.5 mg every 48 hours	0.15 mg once daily **OR** 0.5 mg every 72 hours	0.05 mg once daily **OR** 0.5 mg every 7 days
ETV (decom-pensated liver disease)	1 mg once daily	0.5 mg once daily **OR** 1 mg every 48 hours	0.3 mg once daily **OR** 1 mg every 72 hours	0.1 mg once daily **OR** 1 mg every 7 days
TAF	25 mg orally once a day	25 mg orally once a day	25 mg orally once a day CrCl at least 15 mL/min: no adjustment recommended. 25 mg once daily	CrCl less than 15 mL/ min) not receiving chronic haemodialysis: not recommended.

- **Assessing and monitoring renal function**
- •1. For people initiating treatment with an estimated CrCl or glomerular filtration rate (**eGFR) <50 mL/min** or **with risk factors** for **renal dysfunction**, including **older age**, **long-term diabetes**, **uncontrolled hypertension** or **severe osteopaenia** or **osteoporosis**, **consider either using ETV instead or avoiding TDF or reducing the dose of TDF**

- 2. Use of **TDF** should be **avoided** with **concurrent nephrotoxic drugs** (such as **aminoglycosides**, **amphotericin B**, **foscarnet**, **ganciclovir**, **vancomycin** and **cidofovir**) because of the increased risk of reducing renal function.

- 3. **Monitoring renal function** during **nucleoside analogue** therapy may include:
- **urine dipsticks** for **proteinuria** and **glycosuria** (in the absence of diabetes or if blood glucose is well controlled), serum **creatinine**, estimated **eGFR** decline, serum **phosphate**, **urine protein- to-creatinine** ratio (or fractional excretion of phosphate, if available) as well as **growth** of **children** receiving **TDF**.
- For **individuals** with **normal renal function**, a minimum monitoring package could include **annual urine dipstick** testing and **creatinine** measurement for **eGFR** if possible.

- •4. The frequency of renal monitoring during nucleoside analogue therapy depends on the presence of risk factors for renal dysfunction and should be **more frequent** among **people** at **higher risk.**
- •a. People at high risk of renal toxicity: **every six months** unless there is evidence of worsening. Closer renal monitoring is advisable among people with CrCl <50 mL/min.
- •b. People at low risk of renal toxicity: either no routine monitoring of renal function or **every 12 months** unless there is evidence of worsening.

- 5. **During treatment**, if the **CrCl falls below 50 ml/min** or in case of **progressive decline** of **renal function**, consider **adjusting** the **dosing interval** of **TDF** or **switching** to **ETV** or **TAF** and **closely monitoring renal function**.
- •6. If **low bone mineral density** is **detected** or **suspected** because of a **fracture**, then appropriate consultation should be obtained, with a switch from **TDF to ETV or TAF.**

- **ETV** or **TAF recommended** for **people** with **established osteoporosis** and/ or **impaired kidney function** and also **TAF** in **adolescents** for those **12 years or older,** and **ETV** in children for those **2 years or older**

- **TDF** is mainly eliminated via the **kidney** and has a **side-effect** profile characterized by **proximal tubular cell dysfunction**.
- The range of **severity** is from **mild renal tubular dysfunction** and **hypophosphataemia** with **subclinical decline** in **renal function** to **classical Fanconi syndrome** and impaired **glomerular filtration.**

- **Small decreases** in **bone mineral density** with **osteopaenia** or **osteoporosis** during the **early phases** of **treatment** have also been reported and, **more rarely, lactic acidosis** or **severe hepatomegaly** with **steatosis**.

- **Known risk factors** for **developing TDF-induced nephrotoxicity** include **underlying renal dysfunction**, **low CD4 count** for **people** living with **HIV** and **low body weight** and **comorbid hypertension**, **diabetes**, **HIV-associated kidney disease**, **hepatitis B or C coinfection** and **TDF** in **combination** with a **ritonavir-boosted protease inhibitor**.

- Genetic variability within the **MRP7 gene** may influence **renal tubular transport** of **TDF** and contribute to the **development** of **toxicity**. Although **tubular dysfunction** is **reversible** in **most cases after withdrawal** of **TDF**, **persistent renal dysfunction** has been reported

- **TAF** may also result in **weight gain** and an **increase** in **BMI**.
- Because of the **overall improved renal safety of TAF**, it is preferred to other nucleoside analogues for people at risk of bone or renal complications, **older people** and **people** with **evidence** of **impaired renal function**

- **Children and adolescents**
- **TDF-related decreases** in **bone mineral density** have been observed for children, although it remains uncertain how reduced bone mineral density might affect future **growth patterns** or the risk of **bone fracture**.
- In an **RCT** of **TDF** among **adolescents** (**12–17 years** old),a **6% decrease** in **spine bone mineral density** at **week 72**.

- **careful growth monitoring** is **recommended** while **children** are **receiving treatment** with **TDF**.
- The **safety profile** of **ETV** for **children** was **consistent** with that **observed** for **adults**, with **no reported renal adverse events** over **48 weeks** in an ongoing **ETV trial** reported in an FDA application

- **In pregnancy**
- **TAF** has been **evaluated** in **clinical trials** of **hepatitis B** in **late pregnancy** and appears to be **safe** and **effective**.
- However, although no major safety concerns have arisen in cohort studies, **TAF has not yet been approved** for **PMTCT** of **hepatitis** B

- **Assays to monitor nephrotoxicity**
- . **Data suggest** that **some people** may have **normal serum creatinine levels** but **impaired renal function**, so overreliance on absolute serum creatinine values may lead to TDF administration among people with pre-existing kidney disease.

- A **high frequency** of **glycosuria** has also been found **among people without diabetes** who **underwent** a **biopsy** for **TDF nephrotoxicity**, with **increased serum creatinine compared** with **TDF-treated people** with a **normal GFR**, **suggesting** that **dipstick testing** for **glycosuria** may be a **cost-effective screening test** for **serious TDF-induced kidney injury.**

- **Balance of benefits and harm**
- Although **TDF** is associated with a **risk** of **nephrotoxicity**, **hypophosphataemia** (**especially noted** for **children**), **bone mineral loss** and **osteopaenia**, the **2015 evidence review showed** a **low risk** of **these adverse effects** (ranging from **0.3% to 2%** for **nephrotoxicity**) with **long-term TDF or ETV,** even among people living with **HIV**, but especially in the absence of established risk factors (such as **HIV-associated kidney disease**, **hypertension** and **diabetes**)

- **Switching** from **TDF** to **TAF** maintained or **improved suppression** of **HBV replication** and **improved bone** and **renal safety**, especially for those with **stage 2 chronic kidney disease**.
- **TAF**, the drug is **preferred** to other nucleoside analogues for people at risk of **bone** or **renal complications**, **older people** and **people** with **evidence** of **impaired renal function.**

- •In 2015, the Guidelines Development Group conditionally **recommended annual monitoring** of **renal function**, **growth monitoring** in **children**, **baseline assessment** of **renal function** and categorization of baseline risk of renal dysfunction based on limited evidence.
- **TAF** is now **recommended** in special circumstances for **people** with **established osteoporosis** and/or **impaired kidney function** and also as an **alternative regimen** for **adolescents (aged 12 years or older)**

- The **use** of **TAF** or **ETV** is **recommended among people** with **impaired eGFR** at **baseline (<50 mL/min)** and **other people** at **higher risk** of **renal toxicity** (those who are **older** or have **underlying renal disease**, **long-term diabetes** or **uncontrolled hypertension** or are receiving **concomitant therapy** with boosted **protease inhibitors** or **nephrotoxic drugs**) or those with **evidence** of **worsening** of **renal function during treatment**.

- **Resource considerations**
- **Measurement** and **long-term monitoring** of **serum creatinine** and **bone mineral density** scanning **increases** the **costs** of **care** and **treatment**.
- Access to testing for creatinine may be limited in some settings, and simple **urine dipstick testing** is a **simpler** and **cheaper** alternative in **low- and middle-income countries**.

- **Implementation considerations**
- **Known risk factors** for **developing TDF-induced nephrotoxicity** include **underlying renal dysfunction, low CD4 count**, **low body weight** and **comorbid hypertension**, **diabetes**, **HIV- associated kidney disease**, **HIV** or **C coinfection** and **TDF** in **combination** with a **ritonavir-** boosted protease inhibitor in people with **HIV infection**.
- People receiving TAF should be monitored for **weight gain and lipid rises** as well as metabolic syndrome.

- **Age** and **advanced liver disease** are **additional contributing factors** that can help identify those at **greatest risk** of **osteoporotic fracture**. **Dual-energy X-ray absorptiometry** can be used to monitor **bone mineral density changes** for **people** receiving TDF.
- The frequency of monitoring will depend on each person's **age** and **health status.**