World Health Organization

Service Delivery and Operational Research Agenda for Advancing Progress towards HBV and HCV Elimination

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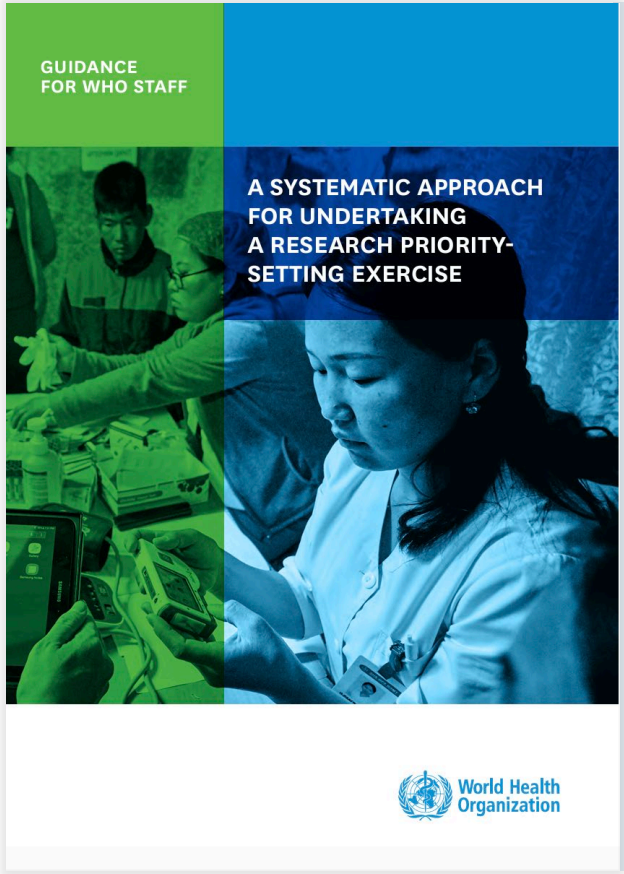
Global HIV, Hepatitis and STIs Programmes
WHO HQ, Geneva
CROI 2024

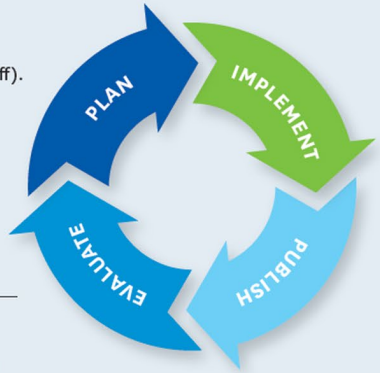
WHO Approaches to Research Priority setting



Overview: a systematic guide for WHO staff when setting research priorities

PLAN

- Define the objective - what change do you want to make and why?
- Who are the priorities for and in what context?
- Identify resources (time-finance-staff).
- Review what has been done before.
- Design a method to match your context – ask RFH unit for help.
- Review to ensure all sections are aligned.



IMPLEMENT

- Decide who needs to be involved - be representative and inclusive in line with context – think about local, economy, enquity and gender.
- Involve stakeholders to agree the priority criteria (e.g. public health benefit, feasibility, cost, timescale).
- Agree method for selecting priorities (e.g. consensus versus metrics).

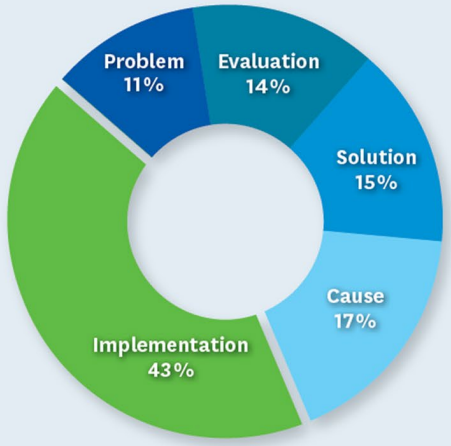
EVALUATE

- Decide on an evaluation plan to measure impact.
- From the plan, monitor the changes you wanted to see: awareness, uptake, translation, impact (e.g. +/- funding flows, improved public health).

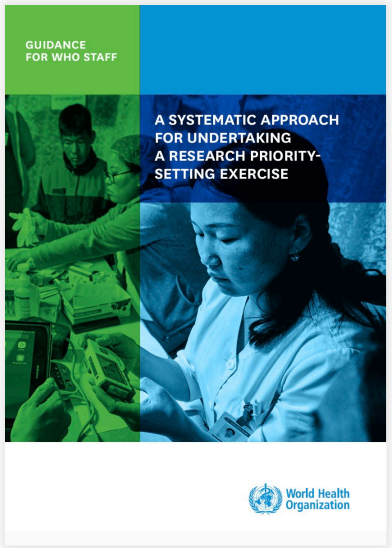
PUBLISH

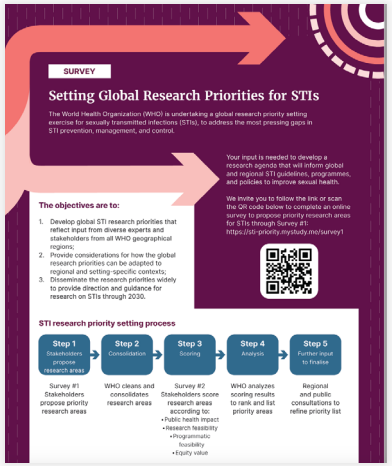
- Develop a dissemination strategy to maximize awareness and uptake.
- Be transparent: publish a clear report that describes the methods used and the stakeholders involved.

Distribution of WHO research priorities by research type (n=2145) extracted from WHO publications published 2002−2017



WHO Approaches to Research Priority setting





Essential National Health Research (ENHR) approach
(published 2009)

Combined Approach Matrix (CAM)
(published 2009)

Child Health and Nutrition Research Initiative (CHNRI)
(published 2006)

James Lind Alliance Priority-setting Partnerships (PSPs)
(current)

Delphi techniques
(since 1950s)

Distinctive Features of WHO Guidelines

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Feature	WHO Guidelines	Other Guidelines
Settings	• Low- and middle-income countries • Generalised/concentrated epidemic settings	• High-income countries
Target audience	• National Program Managers	• Treating clinicians
Approach	• The "public health approach" • Simplified and standardized approaches • Preferred regimens	• Individualized treatment • Multiple treatment options
Formulating recommendations: Evidence-based approach	• GRADE - Feasibility, equity, end-user acceptability, resource use considered	• Variable use of evidence-based framework
Guidelines Committee representation	• 50% LMICs, programme managers, civil society	• Clinicians and researchers HICs

New Directions – Updating WHO hepatitis B guidelines 2024

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Who to treat?

- Expanding criteria for treatment (lower APRI score >0.5 and HBV DNA threshold >2000 IU/ml)
- Expanding treatment for adolescents (immune tolerant)

First-line treatment

- TAF and dual therapy (TDF/3TC or FTC) vs. TDF

PMTCT

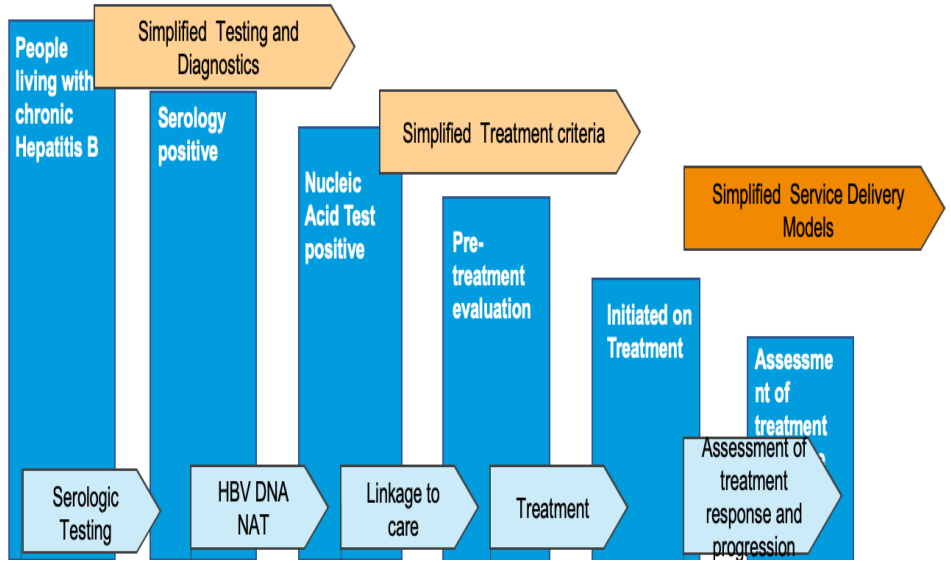
- Expanding criteria for use of antiviral prophylaxis to all HBsAg positive pregnant women, where no access to HBV DNA testing

Simplifying diagnosis

- Use of PoC HBV DNA viral load and reflex viral load testing
- Delta virus testing – Who to test and how to test and reflex testing

Simplifying service delivery

- Good practice principles for promoting adherence and retention in care
- Decentralisation, integration and task-sharing



29 Recommendations
14 New (including updated)

2015 → 2024 – NEW

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ALGORITHM OF WHO RECOMMENDATIONS ON THE MANAGEMENT OF PERSONS WITH CHRONIC HEPATITIS B INFECTION[a]

HBsAg positive

CIRRHOSIS
- Clinical criteria[b]
- NITs (APRI score >2 in adults or FibroScan)

Yes / **No**

ASSESSMENT FOR TREATMENT

AGE[c] >30 years (in particular)

- **ALT[d,e]** Persistently abnormal
  - **HBV DNA** >20 000 IU/mL
  - **HBV DNA** 2000–20 000 IU/mL
  - **HBV DNA** <2000 IU/mL
- **ALT[d,e]** Intermittently abnormal
- **ALT[d,e]** Persistently normal

AGE ≤30 years

- **ALT[d,e]** Persistently normal
  - **HBV DNA** <2000 IU/mL

INITIATE NA THERAPY AND MONITOR
- Tenofovir or entecavir
- Entecavir in children aged 2–11 years

DEFER TREATMENT AND MONITOR

MONITORING

Every 6 months	**DETECTION OF HCC[f]** (persons with cirrhosis or HCC family history)
Every 12 months	**DISEASE PROGRESSION AND/OR TREATMENT RESPONSE IN ALL[f]** • Adherence at each visit, if on treatment • ALT, HBV DNA and HBeAg • Clinical criteria and NITs (APRI in adults or FibroScan)
Baseline and every 12 months	**TOXICITY MONITORING IN PERSONS ON TREATMENT** Renal function[g] and risk factors for renal dysfunction

STOPPING TREATMENT

CIRRHOSIS
Lifelong treatment

NO CIRRHOSIS
- **and** HBeAg loss and seroconversion to anti-HBe and after completion of at least one additional year of treatment
- **and** persistently normal ALT
- **and** persistently undetectable HBV DNA

ALGORITHM OF WHO 2024 RECOMMENDATIONS ON THE MANAGEMENT OF PERSONS WITH CHRONIC HEPATITIS B INFECTION[a]

HBsAg positive

INITIAL ASSESSMENT

ASSESSMENT FOR TREATMENT ELIGIBILITY
1. **Severity of liver disease** eg. non-invasive tests (APRI or transient elastography)
2. **ALT and HBV DNA level**
3. **Medical history:** Screening for presence of resence of coinfections (eg. HIV, HDV or HCV), comorbidities (eg. diabetes, steatotic liver disease) immune suppression (eg. long term steroids, transplant), extrahepatic manifestations (eg. glomerulonephritis, vasculitis), or family history of liver cancer or cirrhosis

GENERAL CARE MEASURES
1. **Counselling on lifestyle** eg. alcohol consumption, diet and physical activity
2. **Preparation for starting treatment** eg. adherence support, risk factors for renal dysfunction[b] and baseline renal function (as indicated)
3. **Preventive measures** eg. HBsAg screening of family members and sexual contacts with HBV vaccination of those negative

TREATMENT ELIGIBILITY

TREAT ALL ADULTS and ADOLESCENTS (aged ≥12 years[c]) (including women and girls of reproductive age) **WITH:**

1. **SIGNIFICANT FIBROSIS (≥F2) or CIRRHOSIS (F4)** (regardless of HBV DNA or ALT levels
   - Clinical criteria for cirrhosis[d]
   - Non-invasive tests: **APRI >0.5** or **transient elastography>7 kPa** (adults)[e]

OR

2. **HBV DNA>2000 IU/mL AND ALT level > ULN[f]**

OR

3. **PRESENCE OF of any of following** (regardless of APRI score, HBV DNA or ALT level)
   - **Coinfection** (eg. HIV, HDV, HCV)
   - **Family history** of liver cancer or cirrhosis
   - **Immune suppression**
   - **Comorbidities** (eg. diabetes, metabolic-associated steatotic liver disease)
   - **Extrahepatic manifestations** (eg. glomerulonephritis or vasculitis)

OR

In absence of access to HBV DNA assay

4. **PERSISTENTLY ABNORMAL ALT LEVELS ALONE[f]**

ALT Persistently normal[de]

AND

HBV DNA <2000 IU/mL

AND

Absence of coinfections, comorbidities, immune suppression, extrahepatic manifestations family history of liver cancer or cirrhosis

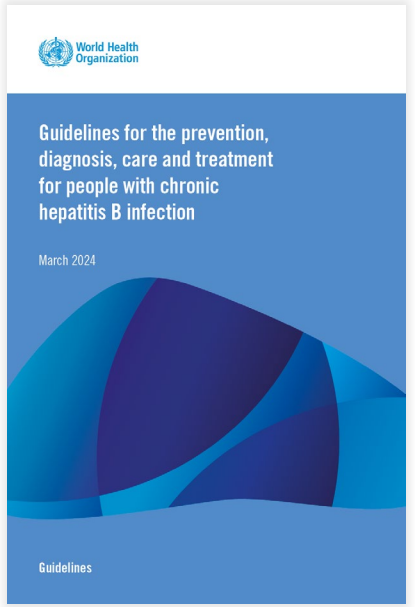
ANTIVIRAL TREATMENT REGIMEN

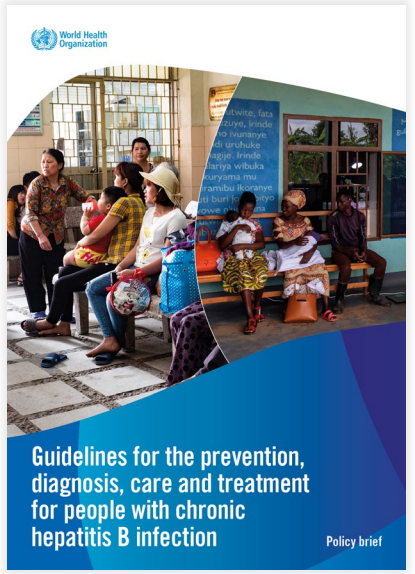
INITIATE ANTIVIRAL THERAPY AND MONITOR[g]
- **TDF or ETV**
- **TDF + 3TC or FTC** (if no access to TDF monotherapy)
- **ETV or TAF** in persons with osteoporosis or impaired kidney function or in children and adolescents

DEFER TREATMENT AND MONITOR

MONITORING[g]

Every 6 months	**DETECTION OF HCC** (AFP and ultrasound) (persons with cirrhosis or family history of liver cancer or cirrhosis)
Every 12 months	**TREATMENT RESPONSE AND/OR DISEASE PROGRESSION[f]** • Adherence at each visit, if on treatment • Non-invasive tests (APRI or transient elastography) • ALT and HBV DNA level • Monitoring of renal function (creatinine), as indicated





Commissioned reviews, modelling and surveys provided a key evidence base for the WHO HBV Guidelines update

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1	Use of non-invasive tests	University College London
2a/2b	Who to treat Natural history and treatment effectiveness according to VL and ALT	Institut Pasteur
3	MTCT rate	Imperial College, University of Liverpool
4	TAF and dual therapy (TDF/XTC)	University of Liverpool
5a/5b	POC HBV DNA (diagnostic performance and clinical impact)	University of north Carolina
6	Reflex HBV DNA viral load	University of north Carolina
7a/7b and 8	Delta testing: Who to test and how to test; Delta reflex testing	WHO and University of north Carolina
9	Simplified service delivery (HIV) (adherence, retention, refill and visit frequency)	Washington University in St. Louis
10 and 11	Simplified service delivery (models of care)	University of Liverpool/All India Institute/Harvard

15 Systematic reviews

Landscaping, access and costs

1	HBV diagnostics	CHAI
2	Delta serology and molecular tests	CHAI
3	TAF and dual therapy	CHAI

Modelling

1	Proportion eligible and impact of expanded treatment eligibility	CDA
2	Antiviral prophylaxis for all HBsAg mothers	Imperial College
3	Numbers needed to treat – viral load threshold	Institut Pasteur

Acceptability, values and preferences 4 surveys and 3 literature reviews

1	Health care worker – survey	ICE-HBV
2	Paediatricians – survey	PENTA
3	MOH Programme managers – survey	WHO
4	Community – survey	HepB Foundation/WHA
5	Community – Literature review Africa	University of Ghana
6	Community – Literature review Asia	University of Melbourne
7	Community	Hep B Foundations

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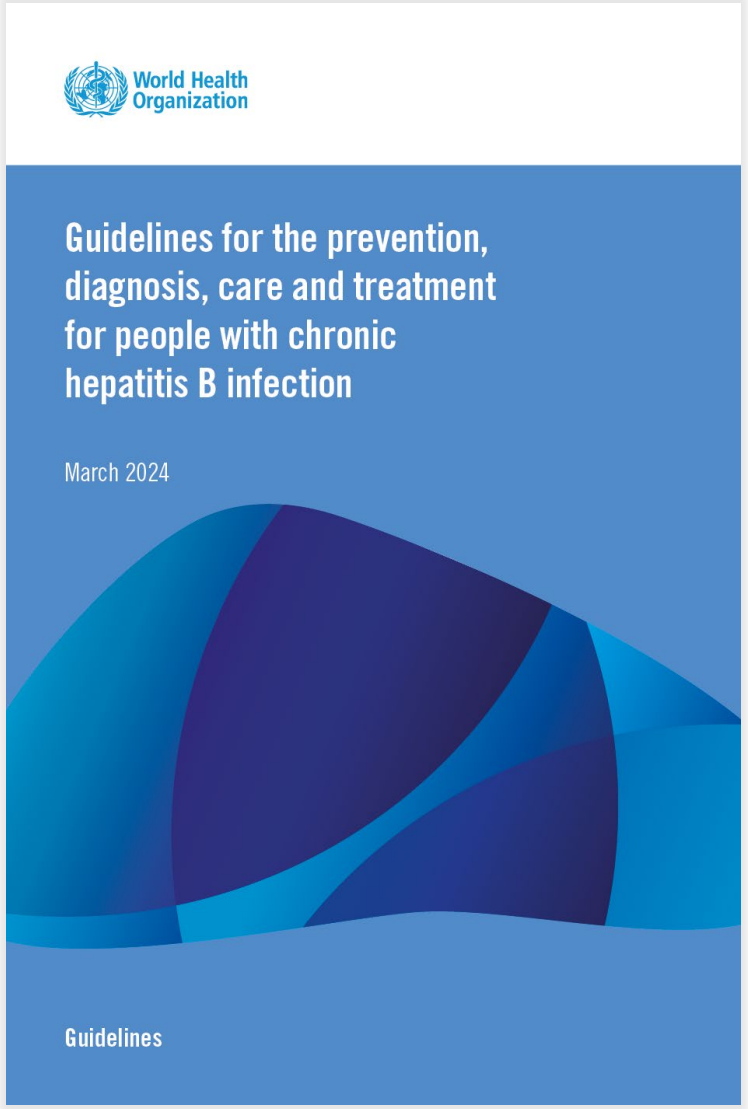
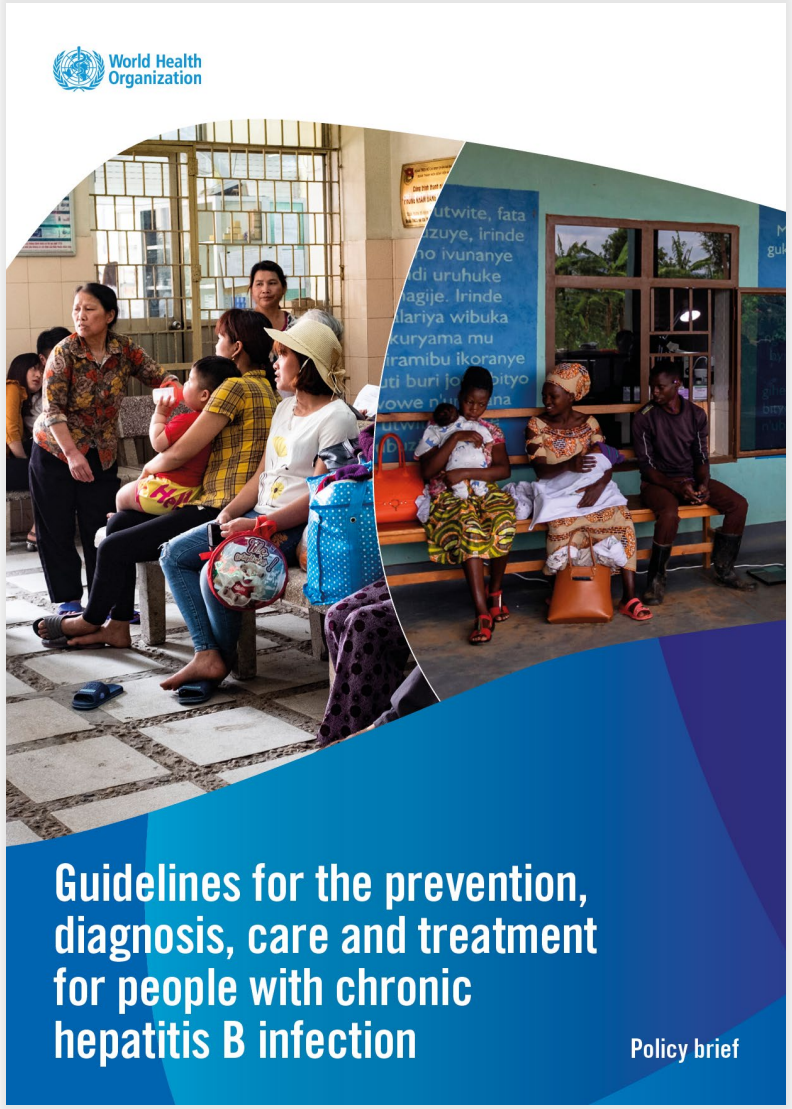
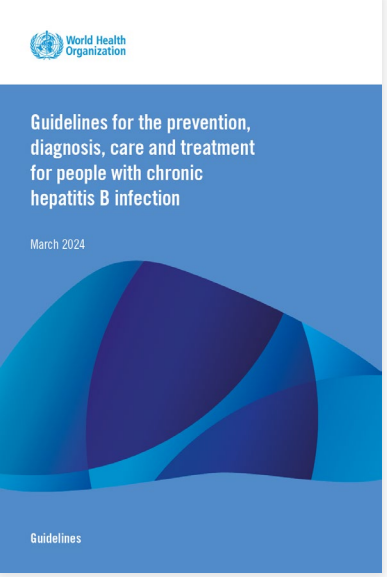
Research Priorities 2024 HBV Guidelines







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RESEARCH AGENDA – HBV

- Surveillance for HCC
- Use of non-invasive tests
- Monitoring
- Who to treat
- Simplified service delivery
- First-line antiviral regimens
- Delta testing: Who to test and how to test
- Use of antiviral prophylaxis for PMTCT
- Reflex HBV DNA testing
- Treatment of adolescents and children
- Point-of-care HBV DNA testing

HBV RESEARCH PRIORITIES – Who to treat?

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- **Long-term studies of overall impact and effectiveness of expanding treatment eligibility** on morbidity and mortality, transmission, quality of life including stigma and potential harms.
- Priority for studies in **low- and middle-income countries**, especially in sub-Saharan Africa but also in **under-researched populations**, such as children, young adults and pregnant women with CHB.
- **RCTs of antiviral therapy** to establish treatment impact among people with **low-level viraemia** and early fibrosis stages, especially in SSA.
- **Long-term prospective cohort studies** to establish a **minimum treatment duration** and period of viral suppression needed to achieve some level of **reduction of disease progression** and development of HCC.
- Longitudinal studies to **evaluate cut-offs for abnormal ALT** in a range of settings and populations and prognostic significance of persistently normal ALT levels despite high HBV DNA levels among people with CHB in sub-Saharan Africa and Asia.

HBV RESEARCH PRIORITIES – PMTCT

- **Evaluate feasibility, effectiveness and cost–effectiveness of maternal peripartum antiviral prophylaxis (universal or high HBV DNA driven) ± timely birth dose vaccine,** especially in settings eg. home births, where access to BD limited.

- **Studies of antiviral prophylaxis adherence,** discontinuation rates, adverse outcomes and uptake of onward referral for treatment assessment.

- Follow-up studies to examine **benefits and potential harm of discontinuing vs. continuing antiviral therapy postpartum.**

- **Assess feasibility and effectiveness of different integrated and simplified antenatal HBV service delivery models and treatment + triple HIV, syphilis and HBV elimination models.**

HBV RESEARCH PRIORITIES – Children and Adolescents

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Who to treat?

- **Burden and routes of transmission** of HBV among children and adolescents in different regions including among higher-risk groups, including among adolescents who inject drugs who have sex with men.
- **Prevalence and progression** of liver fibrosis during childhood
- **Validating thresholds of non-invasive tests** for liver fibrosis staging.

Antiviral regimens

- **Comparative trials and long-term follow-up studies to assess impact of treatment** on development of liver fibrosis, cirrhosis or HCC during adolescence or early adulthood but also HBV transmission and health-related quality of life.
- **Long-term prospective studies to assess potential adverse effects** of long-term antiviral treatment on kidney and bone health, including any effect on peak bone mass achieved during teenage years and lifetime fracture risk.
- **Optimal strategies to promote and maintain adherence** among adolescents and children and minimize risks of clinically silent hepatitis flares.

2022 HCV GUIDELINE RECOMMENDATIONS

Decentralization, Integration and Task-shifting

Moving treatment and care out of speciality clinics

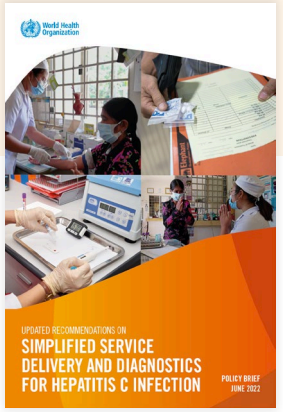
Decentralization:
We recommend delivery of HCV **testing** and **treatment** at peripheral health or community-based facilities, and ideally at the same site, to increase access to diagnosis, care and treatment.
These **facilities** may include primary care, harm reduction sites, prisons and HIV/ART clinics as well as community-based organizations and outreach services.

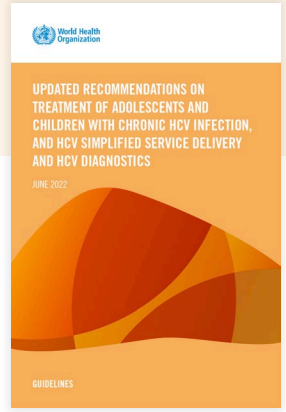
Integration:
We recommend integration of HCV **testing** and **treatment** with existing care services at peripheral health facilities.
These **services** may include primary care, harm reduction (needle and syringe programme (NSP)/opioid agonist maintenance therapy (OAMT) sites), prison and HIV/ART services.

Strong recommendation/ moderate certainty of evidence (PWID/prisoner)
low (general population, PLHIV)

Task-sharing: We recommend delivery of HCV **testing, care and treatment** by trained non-specialist doctors and nurses to expand access to diagnosis, care and treatment.

Strong recommendation/ moderate certainty of evidence





RATIONALE for HCV Recommendations on Decentralization, Integration and Task-sharing

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Evidence review

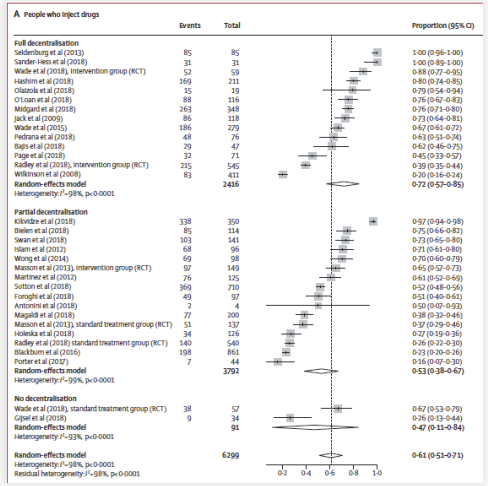
- 142 studies from 33 countries (14%) LMICs) compared full decentralization/integration vs. partial decentralization or none, and task-sharing to non-specialists.
- Increased uptake of HCV viral load testing, linkage to care and treatment among people who inject drugs and prisoners for full decentralization/integration.
- Comparable SVR12 cure rates between specialists and non-specialists across all populations and in all settings

Acceptability by end-users

- Three related surveys and a series of in-depth interviews showed strong support for fully decentralized and integrated HCV services offering testing and treatment at same community site and near to people's homes rather than in hospitals.
- Importance of a non-judgmental/non-stigmatizing approach among health care providers highlighted, especially among PWID and PLHIV.

Decentralisation, integration, and task-shifting in hepatitis C virus infection testing and treatment: a global systematic review and meta-analysis

Summary



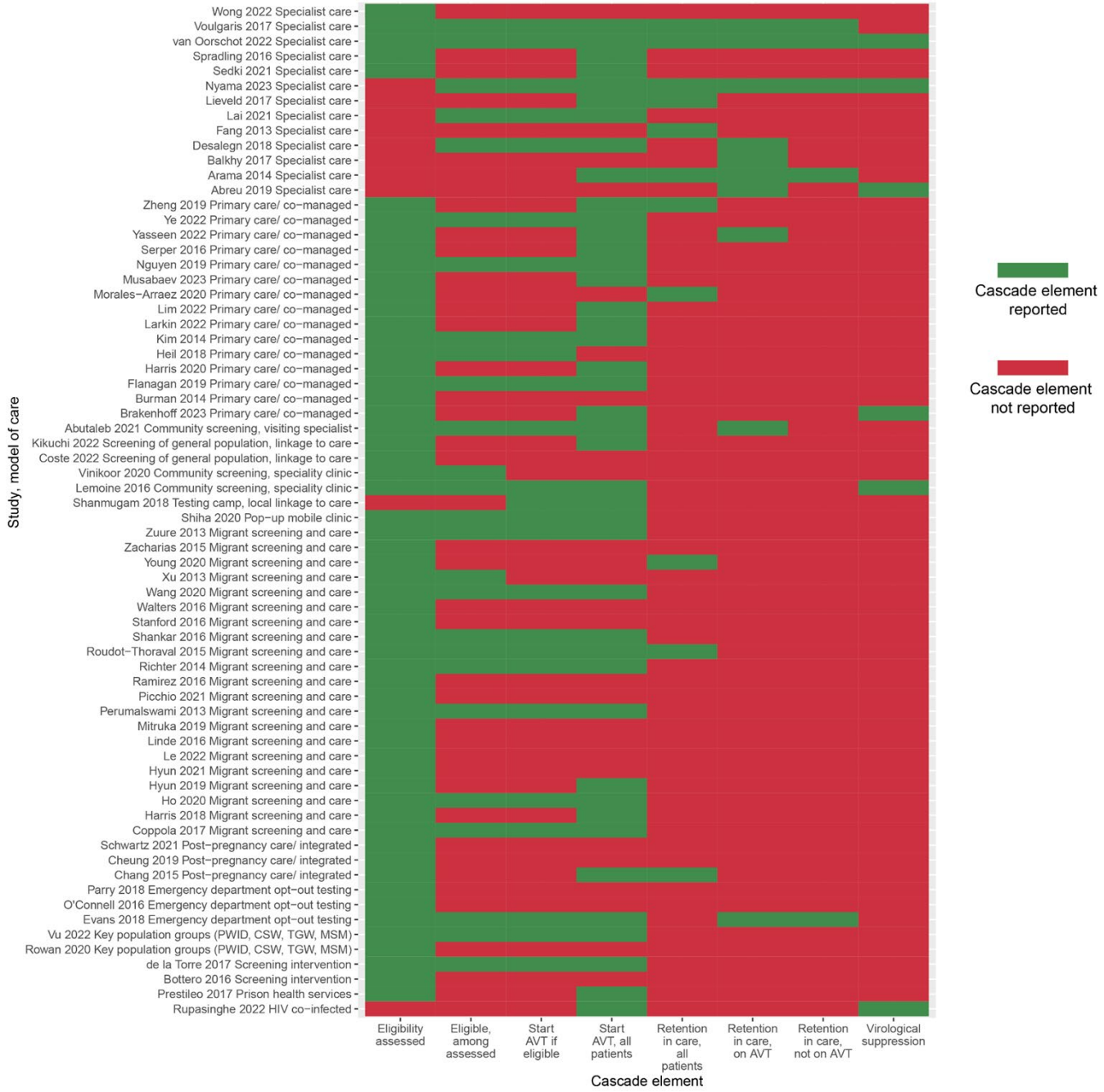
Key messages – HBV service delivery systematic review

Quantitative studies (n=69): reporting of care cascade outcomes

Proportion reporting:

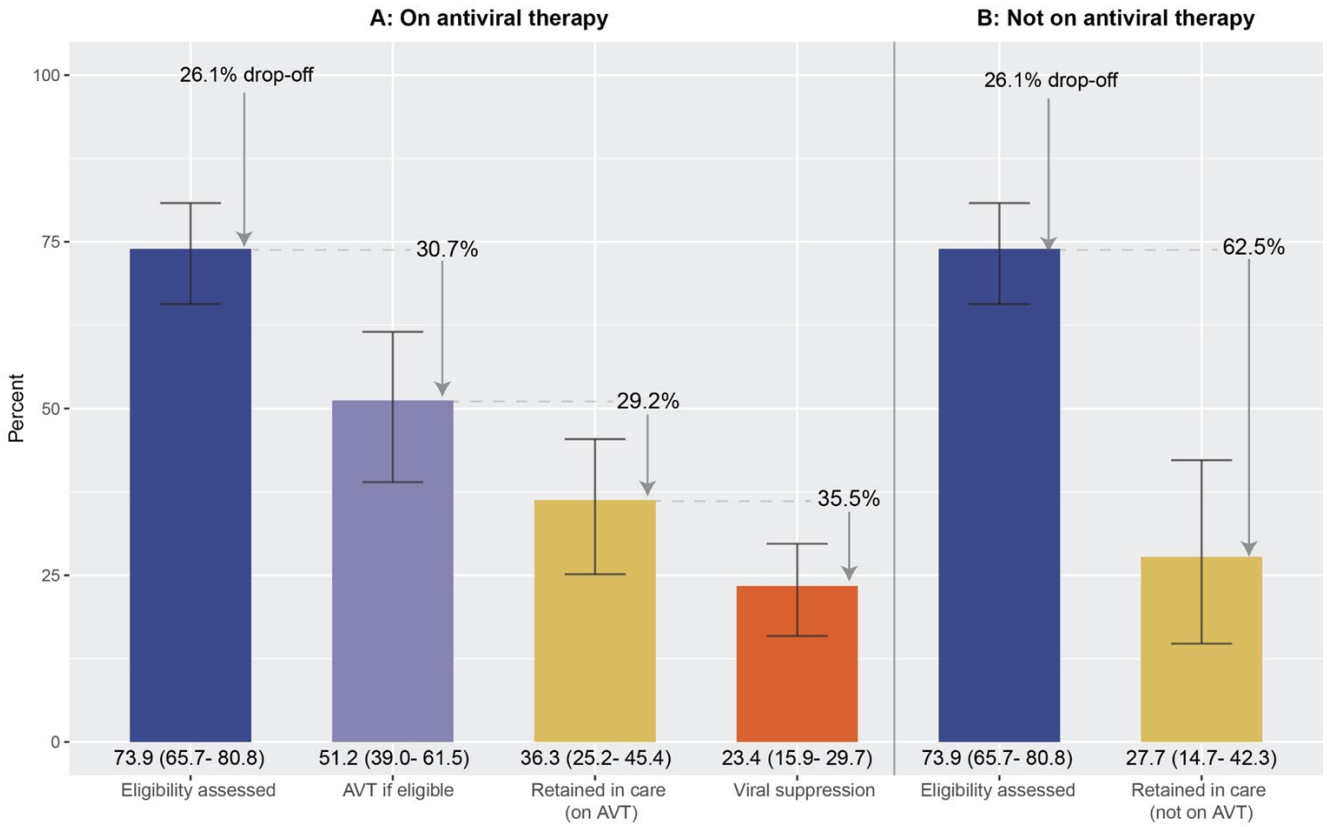
Early cascade (linkage & eligibility)	= 33%
Late cascade (AVT + retention)	= 6%
Complete cascade	= 4%

- Eligibility assessed = 84%
- Meeting treatment eligibility = 39%
- Treatment initiation among eligible = 37%
  Viral suppression = 9%
- Retention = 16%

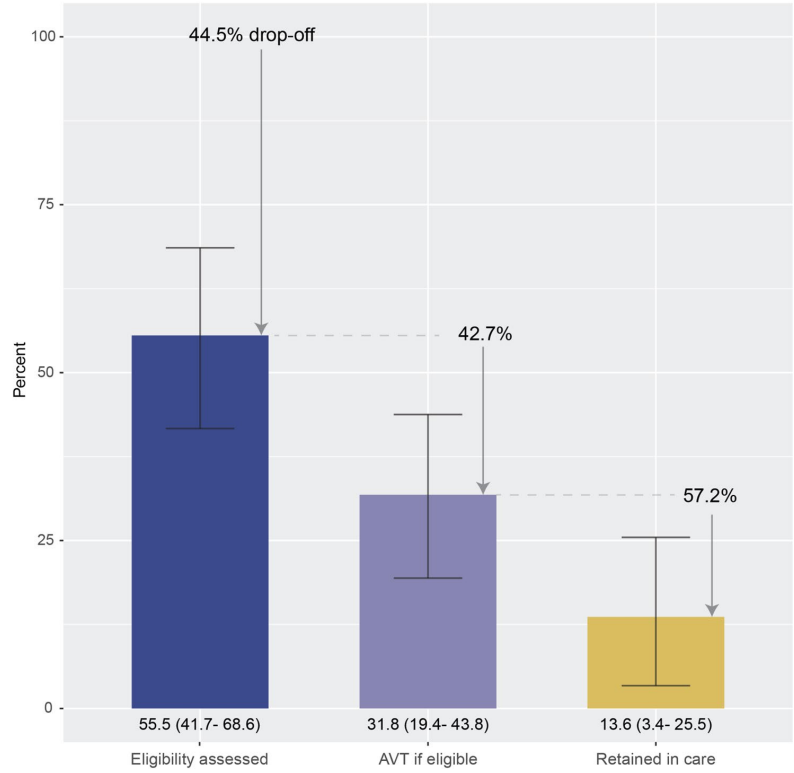


Cascade of care for general population shows low level of DNA suppression and retention in care

Hospital/ specialist care models

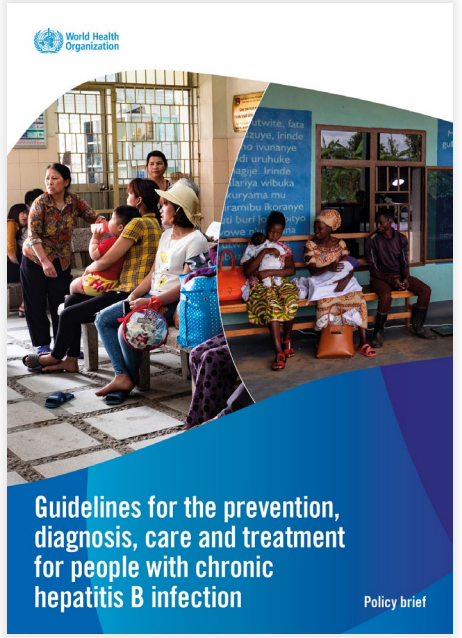


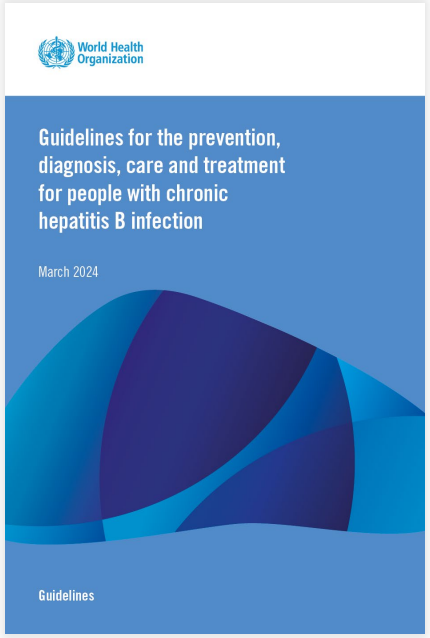
Primary/mixed models



Good practice approaches

1. **Linkage to testing, care, treatment and prevention**
2. **Long term adherence to antiviral treatment**
3. **Retention in care**
4. **Integration of hepatitis testing, care and treatment** with other services
5. **Simplified service delivery**:
   - Decentralization
   - Task sharing
   - Differentiated care
6. **Community engagement**





RESEARCH AGENDA – HBV – Service Delivery

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General principles:

- More methodologically rigorous studies to compare packages of different service delivery models and interventions, especially in LMICs.
- Full description of service delivery model, and capture outcome across entire continuum of care (eg. uptake of testing, linkage to assessment, initiating treatment and retention in care).

- Evaluate Interventions already well established in HIV care to hepatitis B care.
  - **strategies to promote and sustain adherence to long-term antiviral therapy** (eg. peer counsellors, mobile text reminders, cognitive behavioural therapy);
  - **strategies to promote retention in care and re-engage** those disengaged from care (eg. lay counsellors, peer and family support).
  - **strategies to promote the uptake of testing and linkage to care** (eg. dried blood spots; peer and lay health worker support in community-based settings).

- Evaluate different models (including cost/cost–effectiveness data).
  - **decentralized testing and treatment services** in primary care clinics or HIV clinics to promote access to care;
  - **models of integrating hepatitis testing, care and treatment with other services** (such as HIV services and primary care);
  - **task sharing** of activities by different cadres of health-care workers and peer workers;

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WHO Symposium – APASL 2024

Launch of the new 2024 WHO Hepatitis B Guidelines on diagnosis, treatment and monitoring

Co-chairs • Saeed Hamid (Pakistan) • Philippa Easterbrook (WHO)

• Date: Saturday 30 March 2024 • Time: 10.50-12.20 • Place: Room 9, Annex B, Kyoto International Conference Centre

Time	Topic	Speakers
Part 1: New hepatitis B guidelines (45 mins)		
10.50 – 11.30	- Introductory remarks (5 mins)	Meg Doherty (WHO HQ)
	- New WHO hepatitis B guidance on expanded simplified treatment criteria, diagnostic innovations and service delivery – recommendations, evidence-base and rationale (25 mins)	Philippa Easterbrook (WHO HQ)
	- Community perspectives on implementation (5 mins)	Su Wang (Hepatitis B Foundation)
11:30 – 11.40	- Q & A (10 mins)	
Part 2: Implementation challenges and opportunities across the region (45 mins)		
11.40 – 12.15	- Regional overview of current HBV response in WPRO and SEARO (10 mins)	Kiyo Izumi (WPRO) and Polin Chan (SEARO)
	Panel Discussion: Perspectives from countries on new guideline recommendations (30 mins) - China – Jin Lin Hou (Southern Medical University) - Philippines – Janus Ong (University of the Philippines) - India – Shiv Sarin (Institute of Liver and Biliary studies) - Vietnam – Cao Thi Thanh Thuy (Hospital of Hanoi Medical University) - Indonesia – Irsan Hasan (University of Indonesia)	