Viral Hepatitis in low and middle income countries: narrowing the gap

Graham Cooke
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Challenges to the scale-up of treatment for viral hepatitis
Challenges to Treatment of viral hepatitis: lessons from HIV

- Research and surveillance
- Access to services
- Simplification of treatment
- Decrease costs of care
- Patient and community engagement
- Task shifting
- Integration with other services
- Human rights
- Political commitment
- Financing

Ford et al CID (2012)
Research and Surveillance

Making the case for treatment: need
Leading global causes of mortality

1990
- IHD
- Stroke
- LRTI
- COPD
- Diarrhoea
- TB
- Pre maturity
- Lung cancer
- Malaria
- Road injury

24 HCC
1990

2010
- HIV
- Diabetes
- 12 Cirrhosis
- 16 HCC

Comparing the burden of diseases: DALYs

DALYs are a summary statistic covering

- years of life lost (YLL)
- years living with disability (YLD)

For viral hepatitis DALYs are attributed to

- acute infection
- cirrhosis
- HCC

DALYs* attributable to viral hepatitis

<table>
<thead>
<tr>
<th></th>
<th>Acute infection</th>
<th>Cirrhosis</th>
<th>HCC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hepatitis A</strong></td>
<td>4351 (2412-9026)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hepatitis B</strong></td>
<td>4674 (3189-6052)</td>
<td>8990 (7728–10 912)</td>
<td>8938 (7729–10 877)</td>
</tr>
<tr>
<td><strong>Hepatitis C</strong></td>
<td>518 (378-713)</td>
<td>7452 (6370–8553)</td>
<td>4141 (3542–4859)</td>
</tr>
<tr>
<td><strong>Hepatitis E</strong></td>
<td>3715 (1552-7470)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>13258</td>
<td>16442</td>
<td>13079</td>
</tr>
</tbody>
</table>

*1000s

A need to regroup: DALYs

IHD
LRTI
Stroke
Diarrhoea
HIV
Low back pain
Malaria
Pre maturity
COPD
Road injury

23 Cirrhosis
16 Viral Hepatitis
33 HCC

A need to regroup: mortality

IHD
Stroke
COPD
LRTI
Lung cancer
HIV
Diarrhoea
Road injury
Diabetes
TB
12 Cirrhosis
16 HCC
Viral hepatitis

Source: Lozano et al Lancet (2012)
Different objectives for treatment of 3 BBVs

<table>
<thead>
<tr>
<th></th>
<th>HIV</th>
<th>HBV</th>
<th>HCV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TREATMENT</strong></td>
<td>Long-term suppression of viral replication</td>
<td></td>
<td>SVR = Cure Genotypes important</td>
</tr>
</tbody>
</table>
Challenges to programmatic treatment

**AIM OF TREATMENT**

- **HIV**
  - Long-term suppression of viral replication

- **HBV**

- **HCV**
  - Cure

- **(DR) TB**
Example of HBV in Africa

- Research and surveillance
- Simplification of treatment
- Patient and community engagement
# HBV - A Global Health Problem

<table>
<thead>
<tr>
<th>Country</th>
<th>HBsAg+ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>5.3–12</td>
</tr>
<tr>
<td>South Korea</td>
<td>2.6–5.1</td>
</tr>
<tr>
<td>India</td>
<td>2.4–4.7</td>
</tr>
<tr>
<td>Taiwan</td>
<td>10–13.8</td>
</tr>
<tr>
<td>Viet Nam</td>
<td>5.7–10</td>
</tr>
<tr>
<td>Turkey</td>
<td>6.2–8.2</td>
</tr>
<tr>
<td>Africa</td>
<td>5–19</td>
</tr>
<tr>
<td>Russia</td>
<td>1.4–8</td>
</tr>
<tr>
<td>Europe</td>
<td>0.3–12</td>
</tr>
</tbody>
</table>

**HBsAg Prevalence**

- Red: ≥8% – High
- Yellow: 2–7% – Intermediate
- Green: <2% – Low
Transmission of HBV

Vertical transmission (mother to infant)

Childhood transmission

?how

Sexual transmission

Also…

• Injecting drug use
• Blood transfusion/blood products
• Contaminated medical devices/sharps injuries
• Tattooing and body piercing
Tackling viral hepatitis should have a big impact on cancer

In SE Asia

HCC is 3\textsuperscript{rd} most common cancer
China accounts for 55\% of global HCC
70-80\% HCC attributed to chronic HBV infection
Some countries relatively high proportion from HCV (e.g. Japan, Australia, Singapore)

In West Africa

HCC is leading cause of cancer in males, 3\textsuperscript{rd} in women
In West Africa c60\% due to HBV, 20\% due to HCV

Sources: Yuen et al JGH 09, Kirk GD, Hepatology 2004, Perz JF, J Hepatol 2006
Uptake of HBV vaccination
Liver cancer most common cancer in West Africa
• Simplification of treatment
• Reduced costs of treatment
New agents for hepatitis B are simpler to use

- Entecavir
- Tenofovir
Changes to market mechanisms have made drugs affordable

<table>
<thead>
<tr>
<th>Drug</th>
<th>Lamivudine (3TC)</th>
<th>Tenofovir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe (approx price/ppy)</td>
<td>$2600</td>
<td>$4360</td>
</tr>
<tr>
<td>Generic (approx price/ppy)</td>
<td>$21-27</td>
<td>$57-73</td>
</tr>
</tbody>
</table>

Sources: MSF 2012
Patients with HBV monoinfection are neglected

• But can we show feasibility and impact of HBV treatment?
PROLIFICA: PRevention Of LIver FIbrosis and Cancer in Africa

**WATCH** study

*West African Treatment Cohort for Hepatitis B*

**HC$_4$** study

*HCC (HepatoCellular Carcinoma) Case Control study*

EU FP7 (2011-2016) The Gambia, Senegal, Nigeria

MRC/WHO/IARC/Imperial College London

www.prolifica.eu
Study in The Gambia strengthened by GHIS

National trial to examine the impact of HB vaccination on HCC
Primary Objective

- To determine whether treatment of viral hepatitis B reduces the incidence of HCC in West Africa (compared to well characterised established cohorts)

Secondary Objectives

- To enumerate the proportion of the adult population infected with HBV using a community-based screening and a point-of-care test
- To assess the severity of the liver disease in this population
- To evaluate the proportion of the HBV infected subjects eligible for treatment according to the European criteria
- To evaluate whether EASL criteria are applicable in West Africa
WATCH study

Two stages
- Population based screening for HBV (The Gambia and Senegal)
- Non-randomised treatment cohort with a parallel observation cohort

At 5 year follow-up
Hepatitis screening of the population

- Not systematically done in most of SSA
- At risk population are not routinely screened (fewer than 50% of blood banks are tested for HBV and HCV in SSA)
- Expensive (15 euros)
- Not always high quality screening

Sources: Easterbrook, P Semin Liver Dis 2012; WHO 2009
Selected 50 rural and 50 urban West-Gambian areas
Community and individual sensitization
Community-based testing

Participants over 30 years invited to be tested using a POC (Determine, Alere)
Dried-Blood Spots (DBS) are collected at the same time
- Epidemiological and anthropometric questionnaires
- Standard blood tests
- Virological tests
- Liver assessment (USS and fibroscan)

Exclusion criteria:
- HIV +
- HCV +
- Renal failure

Tenofovir
Capacity Building

Clinic

- 2 Junior Gambian MD from RVTH
- 1 Full time Gambian MD

Lab

- 2 Junior Gambian scientists
- 2 Gambian Students
- 1 x Lab Technician for Liver Histopathology
Population screened
Adults > 30 in 30 rural and urban areas N=2,553

Tested for HBsAg N=2,009

544 (21%) DNA
- 178 (33% refusal)
- 232 (41% absent)
- 135 (25% unknown)

HBsAg +ve N=1,857 (92%)

HBsAg –ve N= 152 (8%)
- 34 (28%) DNA clinic
- Enrolled N=118 (78%)

Approx 15% eligible for TDF
HBV: treatment not the main barrier
HCV: Treatment remains a barrier for now
We still choose not to treat many patients with HCV

- Chance of cure (SVR)
  - Improve quality of life
  - Prevent progression to cirrhosis/HCC
  - Prevent transmission

- Chance of failure (no SVR)
  - Serious adverse effects of Rx
  - Quality of life during Rx
  - May have low risk of disease complications
  - Costs – rationed treatments
  - New treatments - sometime…
So – why not do it at scale?

- Risk/benefit of current treatments
- Complexity of care
  - need for skilled practitioners
  - Need for molecular diagnostics
- Costs
- Competing priorities
Do outcomes differ in LMICs for existing treatments?

**Methods:** systematic review and meta-analysis of HCV treatment programmes in LMIC

Data from 12,213 patients included in 93 studies from 17 countries

Ford et al, Bull WHO 2012
Outcomes in LMICs very similar to high income settings

<table>
<thead>
<tr>
<th>HCV genotype</th>
<th>Percentage</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1 or 4</td>
<td>49(43–54)</td>
<td>247</td>
</tr>
<tr>
<td>Not genotype 1 or 4</td>
<td>59(54–64)</td>
<td>247</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Liver damage at baseline</th>
<th>Percentage</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>46(32–60)</td>
<td>343</td>
</tr>
<tr>
<td>No</td>
<td>56(49–63)</td>
<td>287</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HIV status</th>
<th>Percentage</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-positive</td>
<td>23(15–31)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HIV-negative</td>
<td>55(51–59)</td>
<td>203</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level of economic development</th>
<th>Percentage</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low- or lower-middle income</td>
<td>61(56–66)</td>
<td>168</td>
</tr>
<tr>
<td>Upper-middle income</td>
<td>48(43–53)</td>
<td>468</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>WHO Region</th>
<th>Percentage</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>South-East Asia Region</td>
<td>63(52–74)</td>
<td>301</td>
</tr>
<tr>
<td>Eastern Mediterranean Region</td>
<td>55(49–62)</td>
<td>491</td>
</tr>
<tr>
<td>Region of the Americas</td>
<td>38(34–42)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Western Pacific Region</td>
<td>58(40–67)</td>
<td>396</td>
</tr>
<tr>
<td>European Region</td>
<td>54(40–67)</td>
<td>314</td>
</tr>
<tr>
<td>African Region</td>
<td>58(35–81)</td>
<td>217</td>
</tr>
</tbody>
</table>
To what extent will advances in HCV therapy demand scale-up?
How simple do we have to make treatment to scale-up?

IFN – free?

SVR >95%?

FDCs?

12 weeks?

Pan genotypic?

Outcomes in HIV, cirrhotics?
Recent data suggests getting there quickly for G1

Sofosbuvir + Ledipasvir+ Ribavirin
12 weeks
100% SVR 12

ABT 450/r, ABT 333, ABT 267 , RBV
12 weeks
>95% SVR 12

Gane CROI 2013, Poordad NEJM 2013
The G1 world is not enough

Source: Alberti, Liver Int 2011
Should challenge of G3 treatment delay the demand?

POSITRON data from Phase III

12 weeks Sofosbuvir and ribavirin

SVR 12 78%

SVR 93% Genotype 2

SVR 61% Genotype 3

Gilead press release Nov 2012
HIV/HCV co-infection

HCV

- progression accelerated by HIV
- higher rates of all cause, liver and AIDS related death
- poorer response to existing treatments
- 4-5 million co-infected globally
- IVDU in significant proportion

Von Shoen-Angerer et al Lancet 2013
Expertise in lowering prices of ART can be leveraged to co-infection

- negotiate price reductions
- facilitate generic competition
- support quality assurance
- introduce simpler diagnostics
- generate demand forecasts
Financing and Political commitment

UNITAID has co-morbidities within its remit

Some reluctance to take on HCV, under discussion

Precedent for HCV funding within Global Fund as harm reduction

Need for more high quality surveillance data on HCV/HIV co-infection

Ladep et al WJG 2013
Recognising the very different challenges for HCV
Hope for the future
Acknowledgements

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**IARC**
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**WHO**
Nathan Ford

**MSF**
Philipp du Cros

**IHME**
Mohsen Naghavi
10-15% eligible for treatment with tenofovir

<table>
<thead>
<tr>
<th></th>
<th>HBV + n=194</th>
<th>HBV- n=190</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>43</td>
<td>46</td>
</tr>
<tr>
<td>Male (%)</td>
<td>78 (40)</td>
<td>77 (41)</td>
</tr>
<tr>
<td>Elevated transaminases</td>
<td>28 (14)</td>
<td>9 (5)</td>
</tr>
<tr>
<td>Elevated gGT</td>
<td>15 (8)</td>
<td>15 (8)</td>
</tr>
<tr>
<td>Low platelets (%)</td>
<td>19 (11)</td>
<td>17 (9)</td>
</tr>
<tr>
<td>HBV DNA &gt; 2,000 IU/mL</td>
<td>28 (14.5)</td>
<td>NA</td>
</tr>
<tr>
<td>HIV positive (%)</td>
<td>6 (3)</td>
<td>7 (4)</td>
</tr>
<tr>
<td>HCV positive (%)</td>
<td>2 (1)</td>
<td>-</td>
</tr>
<tr>
<td>LSM &gt; 7 kPa</td>
<td>19 (12)</td>
<td>13 (8)</td>
</tr>
</tbody>
</table>
Assessing HBV/HCV infection ...challenging

- Viral Load assessment/Genotyping
  - Not done or expensive: 50,000 CFA = €77
  - Promising innovative techniques (POC and Dry-Blood Spots)

- Liver biopsy is an invasive and costly procedure
- Non invasive markers of fibrosis
  - But still expensive
  - Portable FIBROSCAN (50,000 euros)
EASL treatment guidelines

Consider treatment if:

HBV DNA > 2000 iu/l (~10,000 copies)
and/or ALT > ULN
and evidence of moderate-severe fibrosis

Bearing in mind:
Treatment might not be needed in immunotolerant phase
Mild ALT and mild fibrosis might not require treatment
Compensated cirrhosis may benefit from Rx if ALT and HBV VL low
### EASL treatment guidelines

<table>
<thead>
<tr>
<th>HBV DNA</th>
<th>ALT</th>
<th>Liver Fibrosis</th>
<th>Treat?</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;2000 iu/ml</td>
<td>&gt;40 iu/ml</td>
<td>&gt;5</td>
<td>F&gt;1</td>
</tr>
<tr>
<td>Detectable</td>
<td>&gt;10</td>
<td>F&gt;3</td>
<td></td>
</tr>
<tr>
<td>&lt;2000 iu/ml</td>
<td>&lt;40</td>
<td>≤5</td>
<td>F≤1</td>
</tr>
<tr>
<td>&gt;2000 iu/ml</td>
<td>&lt;40</td>
<td>&gt;5</td>
<td>F&gt;1</td>
</tr>
<tr>
<td>&lt;2000 iu/ml</td>
<td>&gt;80</td>
<td>&gt;5</td>
<td>F &gt;1</td>
</tr>
</tbody>
</table>
Since December 2011, in The Gambia

Community based screening
15 rural areas, 19 urban areas
n = 4,330
Attendance rate: 70% (79% in rural areas, 65% in urban areas)

HBV +
n = 355
P = 8.2%

HBV + from Keneba
N = 168

Visited Liver Clinic
n = 278

n = 3
Refused to participate

HBV + blood donors
N = 20

Objective by the end of 2013
HBV –
n = 238

HBV +
n = 463

n = 701

Objective by the end of 2013
HBV –
n = 800

HBV – from Keneba (>30)
N = 42

n = 77 (21.6%)
Did not attend the clinic yet

HBV – from
Keneba
(>30)
N = 42

HBV –
n = 238
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