Beyond a Focus on Cure: Dissecting the Current HCV Standard of Care sub-Saharan Africa

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Dissecting the Current HCV Standard of Care
sub-Saharan Africa

Majority of HCV-infected individuals in SSA have not been treated
- Previous PegIFN/Ribavirin regimens
- Present standard of care: DAA therapy

Barriers to accessing Standard of Care therapy
- Understanding HCV epidemiology and burden of disease in SSA
- Effective implementation of preventative strategies
- Identification of HCV-infected individuals
  - Access to and cost of diagnostics
- Linkage to care
  - Overcoming barriers of lack of access to Gastroenterologists/Hepatologists
  - Overcoming stigma, discrimination and criminalization
- Access to affordable DAA therapies
  - Affordable generic pangenotypic regimens
  - Simplified treatment algorithms
HCV: Epidemiology

Global HCV viraemic prevalence: 71 (62-79) million people infected
Overall HCV prevalence: 1% (95% UI 0.8-1.1%)

SSA: Overall HCV seroprevalence: 2.98%
• Overall HCV infection (HCV RNA pos) prevalence: 1% (95% UI 0.7-1.6)
• 11 (95% UI 7-16) Million HCV-infected individuals (1% of population)
• Significant regional and national variations in the reported HCV seroprevalence and viraemia and likely modes of HCV infection

HCV Epidemiology : SAA

SSA: Regional prevalence & number of HCV-infected individuals (95% UI)

- **East Africa**: 0.5% (0.4-0.7) : 2.1 M (1.6-2.9)
- **Southern Africa**: 0.7% (0.4-0.9) : 0.5 M (0.3-0.7)
- **West Africa**: 1.3% (1.1-1.4) : 5.1 M (4.3-5.7)
- **Central Africa**: 2.1% (0.1-6.9) : 2.4 M (0.1-8.0)

Data scarce on high-risk populations: MSM, PWID

- Cultural biases or criminalization

**PWID : 8% of global PWID reside in SSA : HCV seroprevalence**

- Tanzania 22.2%, Senegal 39.9%, Ghana 40.1%, Kenya 51.4%, South Africa (57%) and Mauritius 97.3%

**MSM: Few accurate assessments of HCV seroprevalence**

- Sudan: 0.1 to 1%
- South Africa: 3% in HIV negative MSM; 6% in HIV pos MSM in Cape Town

HCV Epidemiology: Incidence in SSA

Table 3 (with map). Incidence of HCV infection in the general population, by WHO region, 2015: 1.75 million new infections in 2015

<table>
<thead>
<tr>
<th>WHO region</th>
<th>Map key</th>
<th>Incidence rate (per 100 000)</th>
<th>Uncertainty interval</th>
<th>Total number (000)</th>
<th>Best estimate</th>
<th>Total number (000)</th>
<th>Best estimate</th>
</tr>
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<tbody>
<tr>
<td>African Region</td>
<td></td>
<td>31.0</td>
<td>22.5–54.4</td>
<td>309</td>
<td>222–544</td>
<td></td>
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<tr>
<td>Region of the Americas</td>
<td></td>
<td>6.4</td>
<td>5.9–7.0</td>
<td>63</td>
<td>59–69</td>
<td></td>
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<tr>
<td>Eastern Mediterranean Region</td>
<td></td>
<td>62.5</td>
<td>55.6–65.2</td>
<td>409</td>
<td>363–426</td>
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<td>European Region</td>
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<td>61.8</td>
<td>50.3–66.0</td>
<td>565</td>
<td>460–603</td>
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<tr>
<td>South-East Asia Region</td>
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<td>14.8</td>
<td>12.5–26.9</td>
<td>287</td>
<td>243–524</td>
<td></td>
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<tr>
<td>Western Pacific Region</td>
<td></td>
<td>6.0</td>
<td>5.6–6.6</td>
<td>111</td>
<td>104–124</td>
<td></td>
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</tr>
<tr>
<td>Global</td>
<td></td>
<td>23.7</td>
<td>21.3–28.7</td>
<td>1 751</td>
<td>1 572–2 120</td>
<td></td>
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</table>
Genotypes 1 and 4 predominate overall, but is pangenotypic (G1-5)

- **Central Africa**: G4 >80% - heterogenous: 4k, 4c, 4r & 4f
- **East Africa**: G1-5 with G4 (50-68%) and G2 (33.3%) predominance
- **Southern Africa**: G1-5 with G5a predominance (35%), G1(31%)
- **West Africa**: G1 (Nigeria 85%) and G2 (Ghana 87%)

Lancet Gastroenterol Hepatol 2017;2: 161
J Viral Hepat 2016; 23: 881
Viral Hepatitis: >135 800 die every year

- **HBV**: 60 M infected: 87 890 deaths
- **HCV**: 11 M infected individuals
  - 37 971 deaths: Cirrhosis & HCC
  - Only 6% living with HCV are diagnosed
  - Only 2% living with HCV access Rx

SSA: Hepatitis B and C related mortality
HCV Transmission Risks: SSA

- Globally, most new HCV infections are in high-risk groups: PWID or MSM

HCV transmission in SSA differs in many aspects to other parts of the world

Traditional practices
- Circumcision or scarification rituals - reused instruments

Iatrogenic
- **Unsafe Blood transfusions:** Late 1990s, only 19% blood screened
  - Risk of acquiring HCV from blood: 2.5 per 1000 units transfused vs 1 per 2-3 million units in high-income countries
  - 2016: 40 WHO Africa region countries: testing 100% blood donations for TTIs
  - Inconsistent confirmatory testing of blood donations remains an issue

- **Unsafe injection practices:** 3.7% in WHO Africa region
  - Reused needles/syringes and injection overuse
    - Vaccination campaigns
    - Parenteral treatment campaigns: Trypanosomiasis (Cameroon)
  - Lack of reuse prevention devices

HCV Transmission Risks : SSA

HIV/HCV co-infection

- 10·8% vertical transmission (High HIV burden)

PWID: 520 000 individuals: Underestimation - increasing population

- Lack of state-funded harm reduction services & reliant on NGO support
  - Needle/syringe exchange & opiate substitution programs (Uganda)

WHO 2030 Target : 300 needle-syringe sets/PWID/year

<table>
<thead>
<tr>
<th>WHO region</th>
<th>Size of the population injecting drugs</th>
<th>Proportion of countries</th>
<th>Needle and syringe distributionc (93)</th>
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</thead>
<tbody>
<tr>
<td>African Region</td>
<td>0.52</td>
<td>0.1</td>
<td>30</td>
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<tr>
<td>Region of the Americas</td>
<td>2.75</td>
<td>0.42</td>
<td>34</td>
</tr>
<tr>
<td>Eastern Mediterranean Region</td>
<td>0.92</td>
<td>0.23</td>
<td>43</td>
</tr>
<tr>
<td>European Region</td>
<td>3.97</td>
<td>0.66</td>
<td>92</td>
</tr>
<tr>
<td>South-East Asia Region</td>
<td>0.56</td>
<td>0.04</td>
<td>82</td>
</tr>
<tr>
<td>Western Pacific Region</td>
<td>3.03</td>
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<td>33</td>
</tr>
<tr>
<td>World</td>
<td>11.75f</td>
<td>0.25</td>
<td>53</td>
</tr>
</tbody>
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Who to Screen? Depends on Prevalence and Transmission Routes

3 approaches

Population screening, including antenatal

Risk-factor based screening

Birth cohort screening

SSA – NO SINGLE APPROACH TO SCREENING (COUNTRY DEPENDENT)

- Risk based screening: PWID, MSM, HCWs, traditional scarification, blood transfusions
- Birth cohort: Cameroon & CAR: mass parenteral infection eradication programs
HCV Screening: SSA

Aim of HCV screening: Identify and ascertain HCV viraemia and link to care
- Only 6% individuals living with HCV are diagnosed

2-step process
- Positive anti-HCV antibody test:
  - Rapid diagnostic tests and laboratory-based immunoassays
- Confirmatory qualitative/quantitative HCV RNA or HCVcAg

Need to retain in care after positive HCV screening

Meta-analysis of HIV testing and care cascade in SSA
- Median rate of loss to follow up after HIV diagnosis was 41% (12-65%)

Point-of-care CD4 cell testing in resource-limited settings
- Shortened the time to and increased initiation of ART

Test and Treat: Further improves retention in care

Use of Primary Health care staff to deliver therapy
- Apply lessons learnt from HIV to HCV care

HCV Screening : SSA

2-step process diagnostic process

Rapid diagnostic tests

• Simple with rapid turnaround within minutes

• **Point-of-care testing:** Enhance linkage to care and reduce loss to follow-up
  - Blood-based (capillary whole blood): US$ 0.50-US$ 2.00
  - Saliva based: US$ 10

• Ideal for programs wishing to upscale rapidly

• **WHO pre-qualified 2 POC RDTs**
  - SD BIOLINE HCV & OraQuick HCV Rapid Antibody Test
  - Comparable performance to 3rd generation EIAs
HCV Screening: SSA

Confirmatory viraemia testing

- HCV RNA nucleic acid testing
  - Qualitative: US$ 43-51; quantitative tests: US$ 30-200
- HCV core antigen (data for G1-3): one-step process
  - Sensitivity impaired < 3000 IU/ml : US$ 25-50
- Need WHO pre-qualified and affordable tests

Pooled testing: Viral hepatitis (HBV, HCV), HIV & tuberculosis services

- Many SSA countries: Cepheid Gene Xpert tests (POC HIV and TB)
- GeneXpert HCV viral load test: Sensitivity of 5 IU/mL, 90 minute turnaround

Public Health Approach

- Offering free TB, HIV, HBV and HCV rapid testing
  - GeneXpert® IV Module Desktop System
  - Fibroscan® 430 Mini: Assess fibrosis
- “Test and treat” approach

Upscale diagnosis and treatment: Reduce cost of diagnostics and needs to be available at primary health care facilities

OPTIMISE PROCUREMENT OF DIAGNOSTICS

Fibrosis Staging: SSA

Staging of patients with fibrosis remains a necessity
• Influences the duration and choice of DAA regimen & need for ribavirin
• Need for HCC surveillance post-DAA therapy

Role of liver biopsy
• Gold standard: Assessing liver fibrosis & establishing potential cofactors
• Invasive, limited availability, high cost, shortage of liver histopathologists in SSA

Non-invasive measures of fibrosis
• **Blood:** APRI, FIB-4, Fibrotest
  - Less discriminatory in accurately staging, good for ruling in or ruling out cirrhosis
• **Vibration controlled transient elastography** (Fibroscan, Echosens)
  - High initial capital cost, annual recalibration, formal training
  - Predictive value for measuring stages of fibrosis validated
  - AUROC >0.85 for assessment of cirrhosis
  - **Applicability as a mobile tool in SSA demonstrated**

APRI score: Recommended blood-based NIT: simplicity and availability
HBV reactivation on DAA: SSA

High prevalence of hepatitis B infection and exposure

- HBsAg prevalence estimate: 6.1%
- HB core Ab positivity: 40-80%
- Screening for HBsAg, HB IgGcAb ± HBV DNA pre-DAA therapy advised
- Monitoring during therapy required

HBsAg positive and meeting criteria for treatment

- Initiate anti-viral therapy

HBsAg positive and not meeting criteria for treatment

- Pre-emptive initiation of HBV antiviral therapy for HBV could be warranted
  - HBV DNA monitoring is expensive and frequently not accessible
Recommended DAA regimens: SSA

Universal access to treatment requires streamlining of therapeutic approaches

• Acknowledge that availability of more complex testing (subgenotyping) might not be readily available

• **Recommended algorithms and DAA regimens:** Allow health-care workers with a broad range of skills to manage patients

Four potential drug combinations: HCV treatment in SSA

• Sofosbuvir/ribavirin
• Sofosbuvir/ledipasvir
• Sofosbuvir/daclatasvir: pangenotypic
• Sofosbuvir/velpatasvir: pangenotypic

Pangenotypic DAA regimens preclude the need for genotype testing

• Sofosbuvir/daclatasvir or sofosbuvir/velpatasvir: Generics available
• Sofosbuvir/ravidasvir (DNDi): DNDi & Egyptian manufacturer Pharco)
**Recommended DAA Regimens : SSA**

**Pangenotypic regimens in SSA**

Optimal for resource-limited settings: Simplifies:

- Diagnosis - no need for genotyping
- Procurement and delivery
- Reduces prescribing and dispensing errors
- Pooled bulk procurement at negotiated prices

DAA regimens need to be registered and be on National Essential Medicines List

<table>
<thead>
<tr>
<th>Genotype 1a/1b</th>
<th>Sofosbuvir and ledipasvir*</th>
<th>Sofosbuvir and daclatasvir†</th>
<th>Sofosbuvir and velpatasvir‡</th>
<th>Sofosbuvir and ribavirin§</th>
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</thead>
<tbody>
<tr>
<td>Treatment naive</td>
<td>12 weeks</td>
<td>12 weeks</td>
<td>12 weeks</td>
<td>No</td>
</tr>
<tr>
<td>Treatment experienced or cirrhosis</td>
<td>12 weeks plus a bodyweight-based dose of ribavirin, or 24 weeks without ribavirin</td>
<td>12 weeks plus a bodyweight-based dose of ribavirin, or 24 weeks without ribavirin</td>
<td>12 weeks</td>
<td>No</td>
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**Genotype 2**

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<th>Treatment naive</th>
<th>Treatment experienced or cirrhosis</th>
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<td>24 weeks</td>
<td>24 weeks</td>
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**Genotype 3**

<table>
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<th>Treatment naive</th>
<th>Treatment experienced or cirrhosis</th>
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<td>24 weeks</td>
<td>24 weeks</td>
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**Genotype 4**

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<th>Treatment naive</th>
<th>Treatment experienced or cirrhosis</th>
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<td>24 weeks</td>
<td>24 weeks</td>
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**Genotype 5**

<table>
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<th>Treatment naive</th>
<th>Treatment experienced or cirrhosis</th>
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</thead>
<tbody>
<tr>
<td>24 weeks</td>
<td>24 weeks</td>
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Decompensated Cirrhosis: SSA

Decompensated Childs-Pugh class B and class C cirrhosis
- Liver transplantation is treatment of choice for end-stage liver disease
- *Liver transplantation not an option in majority of SSA countries*
- Advanced HCV-related liver disease should be considered for DAAs

**SOLAR-1 study: G1 and G4** *(Gastroenterology 2015; 149: 649)*
- Sofosbuvir/ledipasvir for 12 or 24 weeks with ribavirin
  - SVR: 87% (CP-B) and 89% (CP-C): 12 weeks therapy
  - SVR: 86% (CP-B) and 87% (CP-C): 24 weeks therapy

- Childs-Pugh B decompensated cirrhosis with genotypes 1, 2, 3, 4, 6
- Sofosbuvir/velpatasvir: 12 wks with ribavirin: 83% SVR
- Sofosbuvir/velpatasvir: 24 wks without ribavirin: 86% SVR
- **MELD scores >15**: 84% improved scores & 8% worse scores
HIV/HCV Co-infection: SSA

Globally, estimated 2.3 million people of the 36.7 million living with HIV are anti-HCV positive: Odds of HCV infection 6x higher if HIV positive

- anti-HCV positive in HIV-infected individuals: PWID (82.4%), MSM (6.4%), pregnant or heterosexual exposure (4.0%) and general population (2.4%)

SSA accounts for 19% of HIV/HCV co-infected people: 429,600 cases

- Median prevalence: HIV-infected excl PWID: 1% (IQR 1-8): 361 300 cases
- Median prevalence: HIV-infected PWID: 74% (IQR 48-99): 68 300 cases

Lancet Infect Dis 2016; 16: 797
HIV/HCV Co-infection: SSA

Drug-drug interactions with existing ART

• Most ART regimens in SSA: FDC (Tenofovir/emtricitabine/efavirenz)

DAA regimens and EFV-based ART

• **Sofosbuvir/Daclatasvir**: ↑ DCV dose to 90 mg/day
• **Sofosbuvir/Ledipasvir**: Monitor for TDF toxicity
DAA therapy: Chronic kidney disease: SSA

**Prevalence of chronic kidney disease in SSA is substantial**

- Secondary to type 2 diabetes, hypertension and HIV nephropathy
- Mild-to-moderate renal impairment (eGFR >30 mL/min), no dose adjustments required
  - Sofosbuvir/ledipasvir
  - Sofosbuvir/velpatasvir
  - Sofosbuvir/daclatasvir
- **Stage 4 or 5 chronic kidney disease poses a challenge**
  - Access to haemodialysis or peritoneal dialysis is poor
    - Grazoprevir–elbasvir
    - Ritonavir-boosted paritaprevir, ombitasvir and dasabuvir
      - Not widely available nor affordable and are limited to G1 and G4

Clin Nephrol 2016; 86 (suppl 1): 84; Gastroenterology 2016; 150:1590; Lancet 2015; 386: 1537
Hill et al. 2017: Annual net cure of 7% used as a target to reach the WHO target of elimination of HCV as a public health issue by 2030
If 7% of epidemic in 2016 is cured each year (net): >90% people infected in 2016 should be cured by 2030

Access to HCV Therapy

Net cure by region in 2016

- Negative net cure = epidemic size is increasing
- Net cure worldwide in 2016: 0.43%

ESTIMATED 1.1 MILLION PEOPLE TREATED WITH DAA'S IN 2016

SSA (8 countries): 2016 HCV epidemic: 5 069 000
SSA had 34.4 times more new HCV infections than cures
  - 130 800 new HCV infections, 3805 cured & 21 540 HCV-related deaths

Affordability of DAA therapy: SSA

Average yearly income in SSA is US$ 2041 or $5.60 per day

- Three-quarters of the population living on <$2 per day

DAA access pricing for most countries in sub-Saharan Africa

- Individuals bear costs of therapy in many SSA countries, with only a few countries paying for treatment
- Innovative funding mechanisms
- Governments form partnerships with funders
- Pooled procurement mechanisms similar to ART procurement in SSA
  - Generic competition to drive down DAA prices
Gilead/BMS-MPP Licensing Agreements

Costs for 12-week DAA courses

- **Generic Sofosbuvir (400 mg):** US$ 153 in Egypt and **US$ 72 in India**
- **Generic Daclatasvir (60 mg):** **US$ 21 in Egypt** and US$ 183 in India
- **Sofosbuvir/ledipasvir (400 mg and 90 mg):** US$ 307 in India
- **Sofosbuvir/velpatasvir (400 mg and 100 mg):** US$ 350 in India
- **Sofosbuvir/ravidasvir:** <US$ 294 in Egypt
Ensure Linkage to care: SSA

Severe shortage of healthcare workers hinders the equitable delivery of effective and quality interventions for viral hepatitis

- **Africa**: Estimated 2.7 physicians and 12.4 nurses/10,000 pop vs global average of 13.9 physicians and 28.6 nurses /10,000 pop
- **Public health approach**: Integration of HIV, TB & viral hepatitis services
- Combination of seamless and simple screening, diagnostic and therapeutic approaches
  - Enables rapid transition from diagnosis and linked to care
- **Telemedicine distance-learning systems to expand capacity**
- **Smart phone HCV treatment applications (EASL)**
- **ECHO Project (expert hubs and spokes)**: Enables delivery of best-practice care for patients with chronic viral hepatitis in disadvantaged communities
  - “Democratizing” knowledge and practice, by increasing local capacity to identify the disease and treat
  - Implementation in SSA
Global Call for HCV Elimination

Vision: “A world where viral hepatitis transmission is stopped and everyone has access to safe, affordable, and effective treatment & care

• 2020 target: 3 million HCV infections treated

SSA needs to rapidly upscale key interventions to high coverage

• Identification of HCV-infected individuals: affordable, accurate diagnostics
• Linkage to care: Primary (nursing sister driven) to tertiary level care
  ☐ Simple POC diagnostic and treatment algorithms
• Treatment: Sustainable access to affordable pangenotypic DAA regimens
• Prevention:
  ☐ Safe injection practices and safe blood transfusion services
  ☐ Comprehensive harm reduction services for PWID
  ☐ HBV vaccination and safe sex with condom usage

WHO: Towards the elimination of hepatitis B and C by 2030 and WHO Global Hepatitis Strategy, 2016-2021
Political will to recognise Viral Hepatitis as a Health Priority

- Set National Elimination Targets
- Develop National Viral Hepatitis Plans
- Dedicated funding of National Plans
- Universal Access to Treatment
ICVH 2017

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