Building global capacity

Stefano Vella
Center for Global Health
Istituto Superiore di Sanità - Rome
Merck & Co: Global Therapeutic Forum (2015 & 2016)
ViiV: Think Tank – 2015
Gilead: Advisory Board – Tanzania HIV Test & Treat Program - 2016
Janssen: Consultant – TASC (Global Public Health Medical Education Program) - 2016
Viral hepatitis is an international public health challenge, comparable to other major communicable diseases, including HIV, tuberculosis and malaria.

Despite the significant burden it places on communities across all global regions, hepatitis has been largely ignored as a health and development priority until recently.

It will no longer remain hidden, however, with the adoption of the resolution on the 2030 Agenda for Sustainable Development. Target 3 is of particular relevance: it calls for specific action to combat viral hepatitis.
TARGET 3.8: ACHIEVE UNIVERSAL HEALTH COVERAGE, INCLUDING FINANCIAL RISK PROTECTION, ACCESS TO QUALITY ESSENTIAL HEALTH-CARE SERVICES, MEDICINES AND VACCINES FOR ALL

SDG 3: ENSURE HEALTHY LIVES AND PROMOTE WELL-BEING FOR ALL AT ALL AGES

MDG UNFINISHED AND EXPANDED AGENDA

3.1: Reduce maternal mortality
3.2: End preventable newborn and child deaths
3.3: End the epidemics of AIDS, TB, malaria and NTDs and combat hepatitis, waterborne and other communicable diseases
3.7: Ensure universal access to sexual and reproductive health-care services

NEW SDG 3 TARGETS

3.4: Reduce mortality from NCDs and promote mental health
3.5: Strengthen prevention and treatment of substance abuse
3.6: Halve global deaths and injuries from road traffic accidents
3.9: Reduce deaths and illnesses from hazardous chemicals and air, water and soil pollution and contamination

SDG 3 MEANS OF IMPLEMENTATION TARGETS

3.a: Strengthen implementation of framework convention on tobacco control
3.b: Provide access to medicines and vaccines for all, support R&D of vaccines and medicines for all
3.c: Increase health financing and health workforce in developing countries
3.d: Strengthen capacity for early warning, risk reduction and management of health risks

INTERACTIONS WITH ECONOMIC, OTHER SOCIAL AND ENVIRONMENTAL SDGs AND SDG 17 ON MEANS OF IMPLEMENTATION
A few lessons from HIV
World AIDS Conference
DURBAN, 2000

The Global Fund
To Fight AIDS, Tuberculosis and Malaria

Access to medicine

United Civil Society Organisations Coalition on HIV

2001

2004
With significant gains achieved to date, we are on the right side of the tipping point to control HIV, TB and malaria.
Antiretroviral therapy coverage and number of AIDS-related deaths, global, 2000–2015

The impact
MAKE END AIDS by 2030
GOAL NO. 1 IN POST 2015 DEVELOPMENT AGENDA
Seventieth session
Agenda item 11
Implementation of the Declaration of Commitment on
HIV/AIDS and the Political Declarations on HIV and AIDS

On the fast track to ending the AIDS epidemic

Report of the Secretary-General

I. Introduction
Robust progress provides a solid foundation for the fast track
“The AIDS response is at a crucial juncture, both in its immediate trajectory and its sustainability…”

Number of new HIV Infections in LMICs (millions)

- Ambitious Fast-Track targets
- Maintaining 2013 levels of coverage

Source: Adapted from UNAIDS Fast-track Report
For clear, HIV epidemic will rebound without change in coverage by 2020

AIDS transition: low mortality but lower HIV infections
Decrease of HIV new infections: 60% due to ART

- AIDS-related Deaths
- New HIV Infection
Fig. 2.3. The reduction in the annual number of people dying from HIV-related causes has to accelerate to achieve the Fast-Track targets.

- 2005: 2.0 million
- 2000/2010: 1.5 million
- 2015: 1.1 million
- 2020: <500,000
- 2030: <400,000

Source: UNAIDS/WHO 2016 estimates. The red shading shows future targets.
Fig. 2.1. The decline in the annual number of people newly infected with HIV is stalling – and the Fast-Track targets are receding.

Source: UNAIDS/WHO estimates. The red shading shows future targets.
HIV PREVENTION

Male circumcision
- Gray R, Lancet 2007

Female Condoms

Male Condoms

Microbicides for women
- Abdool Karim Q, Science 2010

Oral pre-exposure prophylaxis
- Grant R, NEJM 2010 (MSM)
- Baeten J, NEJM 2012 (Couples)
- Thigpen M, NEJM 2012 (Heterosexuals)
- Choopanya K, Lancet 2013 (IDU)

Treatment of STIs
- Grosskurth H, Lancet 2000

HIV Counselling and Testing
- Coates T, Lancet 2000
- Sweat M, Lancet 2011

Treatment for prevention
- Cohen M, NEJM, 2011
- Donnell D, Lancet 2010
- Tanser, Science 2013

Behavioural Intervention

Needle Exchange
- Drucker E, AIDS 1998

Opioid substitution therapy
- Mathers BM, Lancet 2010

Drucker E, AIDS 1998

Abdool Karim Q, Science 2010

Grant R, NEJM 2010 (MSM)

Baeten J, NEJM 2012 (Couples)

Thigpen M, NEJM 2012 (Heterosexuals)

Choopanya K, Lancet 2013 (IDU)
“Test and Treat” and “Treat All” are great. However, we will never get rid of HIV if we do not address the barriers to testing, access to care, retention, and if we forget to focus on key populations.
Huge progress has been made so far to curb the AIDS epidemic.

A mistake would be to consider this as the “beginning of the end”.

We probably are just at the “end of the beginning”.

From Durban to Durban: end of AIDS further than hoped

The International AIDS Conference in July celebrated the success of antiretroviral treatment (ART) in reducing illness and death.¹ The pall of despair that hung over the the previous Durban conference in 2000 has truly lifted, and in one of the great success stories of global health 17 million people have begun ART. Despite this achievement the mood was sombre as the goal of an end to AIDS receded; but it was also purposeful, and we can do much to bring the goal closer.

We commend the UNAIDS 90-90-90 strategy for fostering testing and linkage to treatment and WHO for guidelines to support it.²³ However, substantial implementation obstacles exist, the greatest of which is that a large proportion of people living with HIV do not know they are infected. In particular, key populations are less likely to access HIV services because of the stigma and discrimination reinforced by laws that criminalise people who inject drugs, men who have sex with men, and sex workers. Even if expanded testing enables us to achieve the first 90 (assuming we know the correct country denominators) and even if patients are retained and adherent for life (regrettably improbable), the 90-90-90 cascade omits 27% of those with HIV. Transmission dynamics are complex, and the 27% left behind most probably include hard-to-reach, stigmatised populations and people with difficult to detect acute primary infection, who together are responsible for most transmissions. The UNAIDS prevention gap report shows new HIV infections stagnating at 2-1 million annually, with many countries experiencing unexpected increases.⁴ IHME’s independent estimates are even higher—74 countries with increased HIV incidence and 2.5 million new infections every year.⁵ In many countries, including Botswana, South Africa, and Swaziland, HIV incidence remains distressingly high, even as we approach or attain the ambitious 90-90-90 treatment goals. Moreover, in a cluster randomised test and treat trial in KwaZulu-Natal, Tasp did not reduce new HIV infections.⁶ True that the HPTN 052 results provide incontrovertible proof of treatment as prevention efficacy among carefully selected stable partners in a meticulously monitored research setting.⁷ But we are not yet seeing, nor should we expect to see, comparable population level effectiveness in the real world. Without underestimating the transformative effects of treatment in reducing AIDS morbidity and mortality and slowing HIV transmission, we will not end this epidemic with tablets alone.

The START⁸ and Temprano⁹ trials finally showed that immediate ART initiation in adults with CD4 counts greater than 500 cells per µL reduces the risk of primary events by 57% compared with deferring ART until CD4 count falls below 350 per µL. The number of deaths, however, was the same in both arms and the absolute difference in the primary clinical endpoint was modest, perhaps because both trials were stopped prematurely.¹⁰¹¹ On balance, the personal health benefits combined with the public health benefit...
Diversity of HIV epidemics: interventions shall be targeted

Figure 4: The importance of location and population
“THE DISPLACED”
SEX WORKERS
DRUG ADDICTION
INCARCERATED
HIV, TB, HCV Syndemics & Prisons as Amplifiers: Semipermeable Membranes
HIV PREVALENCE IN MSM, YEAR 2015
Criminalization of same-sex sexual relations, by country
EXPLOITED YOUNG WOMEN

High rates of HIV among key populations: young women in Africa


Young women have up to 8 times more HIV than men

Source: Adapted from UNAIDS 2012

HIV prevalence in young pregnant women in rural Vulindlela, South Africa (2005-2008)

<table>
<thead>
<tr>
<th>Age Group (Years)</th>
<th>HIV Prevalence (N=1237)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤16</td>
<td>10.6%</td>
</tr>
<tr>
<td>17-18</td>
<td>21.3%</td>
</tr>
<tr>
<td>19-20</td>
<td>33.0%</td>
</tr>
<tr>
<td>21-22</td>
<td>44.3%</td>
</tr>
<tr>
<td>23-24</td>
<td>51.1%</td>
</tr>
</tbody>
</table>
1.5 billion people live in slums
The health of people who live in slums

The history, geography, and sociology of slums and the health problems of people who live in slums


Massive slums have become major features of cities in many low-income and middle-income countries. Here, in the first in a Series of two papers, we discuss why slums are unhealthy places with especially high risks of infection and injury. We show that children are especially vulnerable, and that the combination of malnutrition and recurrent diarrhoea leads to stunted growth and longer-term effects on cognitive development. We find that the scientific literature on slum health is underdeveloped in comparison to urban health, and poverty and health. This shortcoming is important because health is affected by factors arising from the shared physical and social environment, which have effects beyond those of poverty alone. In the second paper we will consider what can be done to improve health and make recommendations for the development of slum health as a field of study.

Introduction

Human beings are undergoing a radical transformation in their ecology.1 During the past two centuries the proportion of the world's population living in cities and towns has grown from about 5% to more than 50%. This process of rapid urbanisation, which started in Europe and North America after the Industrial Revolution in the late 18th century, was accompanied by the development of large slums including famous examples, such as La Chapelle in Paris, France, the Corbals in Glasgow, Scotland, and Khitrov in Moscow, Russia. The past 50 years has seen massive urban growth in low-income and middle-income countries (LMICs) characterised by sprawling slums that are now home to more than half of the population in cities such as Mumbai, India, Nairobi, Kenya, and Mexico City, Mexico.2 This huge growth in slums has provoked increasing international interest, and the United Nations Sustainable Development Goals (SDGs) specify a target to address the "plight of slums".3 The broad purpose of this Series of two papers is to investigate how this goal might be achieved with respect to health. In this first paper in the Series, we first provide some background to slums covering terminology and definitions, the size of slum populations, and the dynamics of their growth. Second, we make a theoretical argument that slum health should be a substantive topic for study, distinct from urban health, and from poverty and health. Third, we examine the extent and nature of previous research in slum health. Fourth, we describe the physical and social factors affecting health in slums. And finally, we describe the particular health problems of people who live in slums, insofar as this can be discerned from the scientific literature.

Terminology and definitions

Concerns have been expressed that the term slum is emotive and pejorative.4 The term informal settlement has been suggested as an alternative. However, the United Nations continues to refer to slums, for example in the SDGs: informal settlement and slum are not synonymous. The United Nations Educational Scientific and Cultural Organisation (UNESCO) defines a slum in terms of an urban space, as "a contiguous settlement where the inhabitants are characterised as having inadequate housing and basic services".5 However, the most widely

Key messages

- The population of slums has increased massively in the past 60 years and slums now dominate many cities in low-income and middle-income countries (LMICs), and are increasing in total population size, especially in Africa.
- Slum health issues are widely subsumed in urban health and the association between poverty and health. Failure to recognise slums as spatial entities obscures neighbourhood effects that are likely to affect health in slums.
- There is an ongoing and unfortunate history of more than 100 years in which people in slums have been marginalised and even stigmatised with the result that they experience the deprivation of property, displacement, and denial of access to basic services.
- People in slums often have just enough money to live on and nothing extra so that if they get ill, they will probably fall into extreme poverty, which in turn leads to worse health leading to extreme inequality and poverty traps.
- Inadequate water supply, sanitation, drainage, and rubbish collection in a crowded environment predisposes to recurrent diarrhoea and diseases such as typhoid, hookworm, and cholera.
- Children are especially vulnerable in slums because of low breastfeeding rates, under-nutrition, and poor sanitation, which predispose children to chronic diarrhoea, stunting, and impaired cognitive development. Studies have reported worse child health in slums than in poor rural areas within the same country.
- Reservoirs and vectors for infectious diseases such as dengue, leishmaniasis, and leptospirosis flourish in slum environments.
- The shared physical and social environment of slums exposes residents to health risks of injury from fire, extreme weather, and crime.
- Insufficient attention has been paid to mental health and non-communicable diseases in stressful slum environments, or to how slum characteristics can affect health outcomes.
- Slum health should be distinguished from urban health and mainstreamed in the implementation of the Sustainable Development Goals and the New Urban Agenda.
Innovations in HIV
(some of them will be good also for HCV)

• Drug development
• Political commitment
• Activism from communities
• Innovative financing
• Health Systems research
• Universal Access & Drug pricing
Antiretroviral Drug Approval: 1987 - 2016

AZT, ddI, ddC, d4T, 3TC, SQV, IDV, NVP, 3TC, SQV, NFV, DLV, RTV, EFV, LPV/r, APV, TDF, ENF, ATV, FTC, TPV, DRV, ETR, RAL, MVC, EVG, DTG, TAF
Long Acting Injectable Nano-Suspensions:

**TMC278LA (Rilpivirine; PATH)**

- NNRTI (Rilpivirine)
- Oral formulation in Complera™
- Long acting: up to 3 months?
- Multiple trials:
  - Dose ranging PK; PK/PD
  - Phase-2: HPTN 076

**Cabotegravir (GSK ‘744; ViiV)**

- Integrase inhibitor
- Similar to Dolutegravir
- Safe in humans with oral run-in
- Activity up to 3 months?
- NHP model efficacy
- Phase 2: Éclair and HPTN 077
Innovations in HIV

• Drug development
• **Political commitment**
• Activism from communities
• Innovative financing
• Health Systems research
• Universal Access & Drug pricing
Innovations in HIV

- Drug development
- Political commitment
- Activism from communities
- Innovative financing
- Health Systems research
- Universal Access & Drug pricing
SILENCE = DEATH
Innovations in HIV

• Drug development
• Political commitment
• Activism from communities
• Innovative financing
• Health Systems research
• Universal Access & Drug pricing
The Global Fund
A 21st-century organization to accelerate the end of HIV, TB and malaria as epidemics

- The Global Fund is the leading contributor of resources in the fight against AIDS, TB and Malaria. It mobilizes and invests nearly US$4 billion a year to support countries and communities most in need. It has an active portfolio of **496 active grants in over 100 countries**, implemented by local experts.

Source: Global Fund grant data as of November 2015
Innovations in HIV

• Drug development
• Political commitment
• Activism from communities
• Innovative financing
• Health Systems research
• Universal Access & Drug pricing
HIV care may inform appropriate response to other health threats

• Demand for services
• Access to services
• Health care workers training
• Support for adherence
• Infrastructure and equipment
• Program management
• Drug and laboratory supplies
• Linkage to care
• Community involvement
How HIV advances in HIV care can inform other health care models

1. Integrated models of care:

   → from HIV,
   → to HIV + TB,
   → to HIV + TB + HIV co-morbidities
   → to HIV + TB + Co-Morbidities + Co-infections (HCV/HBV) + NCDs

2. Differentiated Models of Care:

   → client-centered approach, to simplify and adapt services to reflect the preferences and expectations of various groups of people living with HIV (PLHIV) while reducing unnecessary burdens on the health system.

   → this model could easily also be applied to HCV care
Demedicalizing AIDS Prevention and Treatment in Africa

Tom Ellman, M.B., Ch.B.

At the recent World AIDS Day celebrations, national and organizational commitments to support affected communities, meet treatment and prevention targets, and expand access to antiretroviral therapy (ART) were asserted once again. Yet the reality in much of Africa suggests that AIDS is far from over.

Since 2002, ART programs have been slowly rolled out in Africa. Initially, HIV-infected people had to wait until they were seriously immunocompromised, with a CD4 T-cell count below 200 per cubic millimeter, to begin ART. The threshold was raised to 350 and then 500, as the importance of earlier initiation of treatment was recognized. Improved tools and strategies followed, as did consensus on treatment guidelines and international funding. The trajectory toward ending AIDS seemed assured, and international goals grew from “3 by 5” (treating 3 million people by 2005), to “15 by 15,” to a call from the Joint United Nations Program on HIV/AIDS for “90-90-90” by 2020: 90% of people living with HIV tested, 90% receiving treatment, and 90% with an undetectable viral load.

Close examination of the HIV epidemic, however, reveals that all is not well. In South Africa, home to the world’s largest ART program, for instance, 25% of patients who begin ART are lost to follow-up by a year later, and in 25% of treated patients, viral suppression is not achieved.¹ In many countries, rates of retention in treatment are worsening, the incidence of HIV infection among young women remains shockingly high,² men are tested and initiate treatment late in the course of infection and often not until they have advanced disease, public-sector facilities are overloaded with patients and plagued by medication stock-outs, and donor funding has flatlined for the past 6 years.³ Perhaps most important, the activist groups that have held governments, health systems, and the international com-
Health care worker-managed group

Client-managed group

Facility-based individual

Out-of-facility individual
Innovations in HIV

• Drug development
• Political commitment
• Activism from communities
• Innovative financing
• Health Systems research
• Universal Access & Drug pricing
TRIPS: Trade-Related Aspects of Intellectual Property Rights

• Mandatory patent protection for inventions in all fields of technology for a minimum term of twenty years.

However:

• “Members may, in formulating or amending their laws and regulations, adopt measures necessary to protect public health and nutrition, and to promote the public interest in sectors of vital importance to their socioeconomic and technological development, provided that such measures are consistent with the provisions of this Agreement” (art. 8)
The fall in pricing of HIV medicines, both generic and proprietary, played a crucial role in increasing access to ART in LMIC.

Box 4: Access to medicines and the Doha Declaration on TRIPS and Public Health

Measuring access to medicines is a complex task, but price is one key factor among others. The Doha Declaration on TRIPS and Public Health recognized concerns about effects on prices while noting the need for innovation. Since the Declaration was adopted in 2001, prices for many treatments have fallen significantly, in part due to generic competition and tiered pricing schemes (see graph below). Surveys also show a marked increase in the use of TRIPS flexibilities to promote access to medicines.

**Falling prices of first-line combinations of some first-line anti-retroviral therapies for HIV-AIDS since 2000**

<table>
<thead>
<tr>
<th>Price (US$) per patient per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowest originator US$ 10,439</td>
</tr>
<tr>
<td>Brazil US$ 2767</td>
</tr>
<tr>
<td>Lowest originator US$ 727</td>
</tr>
<tr>
<td>Lowest originator US$ 621</td>
</tr>
<tr>
<td>Lowest originator US$ 555</td>
</tr>
<tr>
<td>Lowest originator US$ 549</td>
</tr>
<tr>
<td>Cipla US$ 132</td>
</tr>
<tr>
<td>Hetero US$ 87</td>
</tr>
<tr>
<td>Aurobindo US$ 159</td>
</tr>
<tr>
<td>Hetero US$ 295</td>
</tr>
<tr>
<td>Hetero US$ 281</td>
</tr>
</tbody>
</table>
Universal access to HIV treatment is one of the greatest success stories in medicine (>17 million treated).

This should not stand alone, but be repeated for mass treatment of cancer, viral hepatitis and other diseases – this time, more quickly.
illions of people around the world do not have access to the medicines they need to treat disease or alleviate suffering. Strict patent regimes introduced following the establishment of the World Trade Organization in 1995 interfere with widespread access to medicines by creating monopolies that keep medicines prices well out of reach for many.

The AIDS crisis in the late nineties brought access to medicines challenges to the public’s attention, when millions of people in developing countries died from an illness for which medicines existed, but were not available or affordable. Faced with an unprecedented health crisis—8,000 people dying daily—the public health community launched an unprecedented global effort that eventually resulted in the large-scale availability of low-priced generic HIV medicines.

But now, high prices of new medicines—for example, for cancer, tuberculosis and hepatitis C—are limiting access to treatment in low-, middle- and high-income countries alike. Patent-based monopolies affect almost all medicines developed since 1995 in most countries, and global health policy is now at a critical juncture if the world is to avoid new access to medicines crises.
Some treatments are simply too important to public health to leave their distribution to the private interests vying against each other......

Taking a broad, public health perspective on access to medications may provide a better context for policy discussions regarding the pricing of breakthrough pharmaceuticals and create opportunities for a virtuous circle for manufacturers, payers, and patients.
Promoting Access to Medical Technologies and Innovation

Intersections between public health, intellectual property and trade
• Procurement interventions
• Pro-generic policies
• Pricing interventions
• (voluntary licensing and patent pools)
• Quality of Generics
• Quality use of medicines
• Trade-Related Aspects of Intellectual Property Rights Flexibilities
Importation of generic hepatitis C therapies: bridging the gap between price and access in high-income countries

Nancy Chimes, Wendy Lipworth, Richard Day, Andrew Hill, Gregory Doran, Mark Dautrebande

An estimated 80–150 million people are infected with hepatitis C virus (HCV) worldwide, with the highest prevalence in low-income and middle-income countries of Africa and Asia. HCV-related liver disease mortality is estimated to be half a million per annum.1

Chronic HCV infections were traditionally treated based on two decades, with the addition of ribavirin, pegylated interferon, and interferon monotherapy, providing sustained virological response (SVR). Despite these improvements, interferon-containing HCV therapy approaches remained highly toxic and costly in many countries, ranging from less than 1% to a maximum of 5% of people with chronic HCV starting therapy each year.2

Fortunately, these past 5 years have seen a revolution in HCV therapeutic development, with the advent of interferon-free DAA therapies, which disrupt replication through inhibition of HCV protease, polymerase, and NS5A function.3 Simple (single daily dosing oral regimens), highly tolerable, short-duration (8–24 weeks) regimens with extremely high efficacy (cure rates >95%) have been developed and registered in 120 countries with 170 combinations depending on HCV genotypes and previous treatments exposure; these include sofosbuvir and ledipasvir,4 parnaptaxel, ribavirin, omnitab, and daclatasvir with or without voxilaparv and elbasvir and grazoprevir.5,6,7,8,9

There is clear evidence that HCV cure alleviates the risk of HCV-related liver disease and hepatocellular carcinoma.10 Early treatments might have greater benefits. Furthermore, as a result of the high efficacy and tolerance, and ease of dose adjustment, HCV therapies as pre-emptive are being explored in some countries, particularly in treatment of high-prevalence populations, such as those with key populations and incarcerated populations.11 The rapid implementation of these therapeutic regimens has the potential to dramatically reduce the burden of HCV-related disease globally. Indeed, new HCV therapies have been deemed so important that some (sofosbuvir, daclatasvir) were added to the 2015 WHO essential medicines list along with a number of other combinations.12

High drug pricing for simeprevir-free DAA regimens (up to US$93,000 per 12-week course) has limited broad implementation in the vast majority of settings.4 Restrictions based on liver disease stage generally introduced to reduce drug impacts.4 Other restrictions, including those based on ongoing drug and alcohol use, have further limited access to many settings, particularly within the USA.12 Even in high-income countries, there is considerable diversity in access and pricing of new HCV therapies.

In the UK, spending on HCV treatments increased almost six-fold between 2014 and 2015, to £190 million.13 Estimates suggest that it would cost more than £4 billion to treat the estimated 214,000 people with chronic HCV in the UK at a cost of £20,000, so access has generally been restricted to those with advanced liver disease. The Australian Government has allocated AU$1 billion to fund HCV DAA therapies for the next 5 years, with no restrictions based on liver disease stage. This is a volume-based pricing deal between the government and pharmaceutical companies.14 Although details are not publicly available, it is understood that this deal is expected to provide treatments for approximately 60,000 individuals. However, there is also a risk-sharing arrangement in place, so that if more individuals are treated than the forecast, the government will compensate the pharmaceutical companies.15

In the United States of America, the price of a 12-week treatment with sofosbuvir and daclatasvir is US$85,000, with no restrictions based on liver disease stage. This is a volume-based pricing deal between the government and pharmaceutical companies.16 Although details are not publicly available, it is understood that this deal is expected to provide treatments for approximately 60,000 individuals. However, there is also a risk-sharing arrangement in place, so that if more individuals are treated than the forecast, the government will compensate the pharmaceutical companies.17

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HIV/AIDS has re-framed medicines from being understood as private goods to global public goods. Second (and relatedly), it has legitimised the idea that public health concerns may trump intellectual property protection.
# Principles of Infection Elimination/Eradication

<table>
<thead>
<tr>
<th>Control</th>
<th>Reduction of infection incidence, prevalence and morbidity/mortality to a locally acceptable level. Continued intervention measures needed.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Diarrhoeal disease</strong></td>
</tr>
<tr>
<td>Elimination</td>
<td>Reduction to zero of the incidence of a specified infection in a defined geographical area. Continued intervention measures needed.</td>
</tr>
<tr>
<td></td>
<td><strong>Poliomyelitis</strong></td>
</tr>
<tr>
<td>Eradication</td>
<td>Permanent reduction to zero of the worldwide incidence of infection. Intervention measures no longer needed.</td>
</tr>
<tr>
<td></td>
<td><strong>Smallpox</strong></td>
</tr>
</tbody>
</table>
WHY

The Global Burden of HCV

- More than 100 million people infected with HCV
- 80 million people with HCV live outside the target high-income markets
- HCV implicated in 28% of cirrhosis and 26% of liver cancer, globally
- At least 500,000 deaths per year

Chung et al, NEJM 2014
The Global Burden of Viral Hepatitis from 1990 to 2013

The Global Burden of Disease Study

1990
1. Ischaemic heart disease
2. Cerebrovascular disease
3. Lower respiratory infections
4. Diarrhoeal disease
5. COPD
6. Tuberculosis
7. Neonatal preterm birth
8. Road injuries
9. Lung cancer
10. Viral hepatitis
11. Malaria
12. Neonatal encephalopathy
13. Alzheimer’s disease
14. Stomach cancer
15. Congenital anomalies
17. Diabetes
18. Hypertensive heart disease
27. Chronic kidney disease
39. AIDS

2013
1. Ischaemic heart disease
2. Cerebrovascular disease
3. COPD
4. Lower respiratory infections
5. Alzheimer’s disease
6. Lung cancer
7. Viral hepatitis
8. Road injuries
9. AIDS
10. Diabetes
11. Tuberculosis
12. Diarrhoeal disease
13. Hypertensive heart disease
14. Chronic kidney disease
15. Malaria
16. Stomach cancer
19. Neonatal preterm birth
20. Neonatal encephalopathy
21. Congenital anomalies

Communicable and neonatal  Non-communicable  Injuries

Stanaway et al, Lancet 2016 in press
FIG. 1.1. Global prevalence of viraemic HCV (reported and extrapolated)

The WHO Viral Hepatitis Elimination Goals

- By 2030
  - 90% chronic HCV diagnosed
  - 80% treated
  - 65% mortality reduction

- Treatment-as-prevention
  - People who inject drugs (PWID)
  - HIV + men who have sex with men (MSM)
Is Elimination of HCV Feasible?

HCV Meets All Established Criteria For Elimination

No non-human reservoir

Virus cannot amplify in the environment

Simple and accurate diagnostic tools

Practical interventions to interrupt transmission

Infection is curable

HCV ERADICATION THERAPY

SHALL IT BE RESERVED TO SPECIAL CLINICAL OR TRANSMISSION CATEGORIES?
### HCV Is More than a Liver Disease. Increased Mortality Beyond the Liver. The REVEAL Study

<table>
<thead>
<tr>
<th>Causes of Death</th>
<th>Multivariate-adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All causes</td>
<td>1.89 (1.66–2.15)</td>
</tr>
<tr>
<td>All liver-related</td>
<td>12.48 (9.34–16.66)</td>
</tr>
<tr>
<td>Hepatocellular carcinoma (HCC)</td>
<td>21.63 (14.83–31.54)</td>
</tr>
<tr>
<td>All extrahepatic diseases</td>
<td>1.35 (1.15–1.57)</td>
</tr>
<tr>
<td>All cancer, except HCC</td>
<td>1.32 (1.00–1.74)</td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>1.50 (1.10–2.03)</td>
</tr>
<tr>
<td>Nephritis/nephrosis</td>
<td>2.77 (1.49–5.15)</td>
</tr>
</tbody>
</table>

Lee et al, J Infect Dis 2012;206:469-77
The Clinical Benefits of a SVR

Family, society, global

Potential benefits of SVR

Economic (direct and indirect)

Hepatic

Reduces:
- Inflammation
- Fibrosis
- Cirrhosis
- Portal hypertension: variceal bleeding
- Decompensation: ascites, hepatic encephalopathy
- HCC

Extrahepatic

Potentially reduces:
- Cryoglobulinemia, B-cell non-Hodgkins lymphoma
- Chronic kidney diseases
- Lichen Planus, PCT, Sjogren’s syndrome
- Insulin resistance and type 2 diabetes
- Stroke risk and myocardial perfusion defects
- Fatigue and depression
- Improves neurocognitive function
- Improves HRQoL and work productivity

Reduces hepatic-related morbidity and mortality

Reduces extra-hepatic-related morbidity and mortality

Reduces all-cause mortality

Terrault & Hassanein J Hepatol 2016
SVR is associated with improved quality of life
Screening and Management Strategies Needed to Satisfy Societal and Medical Needs

**SOCIETAL NEED**

Prioritising high incident populations (PWID) impacts incident infection, but does not stop new cases of severe liver morbidity

**MEDICAL NEED**

Prioritising older patients with advanced liver fibrosis impacts severe liver morbidity, but does not reduce incident transmission

- Need management programmes to address both for optimal impact on HCV prevalence and reduction in HCV-related morbidity and mortality


PWID: people who inject drugs
We need to keep our eyes wide open on transmission dynamics.

**Major Drivers of the HCV Prevalence**

<table>
<thead>
<tr>
<th>Old infections</th>
<th>Resource-rich settings</th>
<th>Resource-poor settings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iatrogenic</td>
<td>Blood transfusion, unsafe medical procedures</td>
<td>Unsafe injections during mass parenteral therapies</td>
</tr>
<tr>
<td>IVDU</td>
<td>Immigration from resource-poor settings</td>
<td>(IVDU)</td>
</tr>
</tbody>
</table>

New infections

*Courtesy from Prof. F. Negro, Geneva 2014*
GLOBAL HEALTH SECTOR STRATEGY ON
VIRAL HEPATITIS
2016–2021
TOWARDS ENDING VIRAL HEPATITIS
Figure 6. Targets for reducing new cases of and deaths from chronic viral hepatitis B and C infection.
Figure 5. The continuum of viral hepatitis services and the retention cascade

VIRAL HEPATITIS CASCADE

ALL PEOPLE
PEOPLE REACHED BY PREVENTION ACTIVITIES
PEOPLE TESTED
ARE AWARE OF STATUS
ENROLLED IN CARE
ON TREATMENT
RETAINED ON TREATMENT
VIRAL LOAD SUPPRESSED
ACCESSING CHRONIC CARE

CONTINUUM OF SERVICES
PREVENTION
TESTING
LINK TO CARE
TREATMENT
CHRONIC CARE
Fig. 3.2. The cascade of HIV services

Source: Global Health Sector Strategy on HIV, 2016–2021 (6).
Hepatitis C: only a step away from elimination?

Globally, an estimated 185 million people are infected with hepatitis C virus (HCV). Acute HCV infections are usually asymptomatic. However, about 75% of patients develop chronic infection, which can lead to liver cirrhosis and hepatocellular carcinoma. 700,000 deaths worldwide could be attributed to HCV in 2013. While most people affected live in low-income and middle-income countries in Asia, Africa, and the Middle East, in the UK an estimated 200,000 individuals are infected with HCV, and annual deaths from HCV have quadrupled since 1996. These figures are appalling. But the extraordinary recent developments in treatment for hepatitis C offer substantial grounds for optimism. A series of new drugs—more effective in viral clearance with fewer side effects—are changing the landscape for hepatitis C.

Today’s Lancet gives a sense of the remarkable past few years it has been for hepatitis C. As described in Daniel Webster and colleagues’ comprehensive Seminars until recently interferon in combination with ribavirin was the main treatment for hepatitis C, but eligibility, safety, tolerability, and effectiveness were limited. The development of direct-acting antiviral drugs towards NS3/4A protease, NS5B polymerase, and NS5A replication complex has progressed tremendously and now allows for interferon-free therapies. Four clinical trials with new regimens are published in today’s issue. The C-WORTHY trial assessed a single-tablet once-daily regimen of glecaprevir (protease inhibitor) and elbasvir (NS5A inhibitor) with or without ribavirin for patients with HCV genotype 1. Eric Lawitz and colleagues report a sustained virological response (SVR) at 12 weeks, irrespective of ribavirin and duration of treatment. Similarly, Mark Sulkowski and colleagues report very encouraging results (SVR at 12 weeks: 92.2%) in patients co-infected with HIV. With about 25% of individuals infected with HIV being co-infected with HCV, inclusion of this group of patients in trials is also of utmost importance. In the PHOTON-2 trial, Jean-Michel Molina and colleagues specifically assessed the recently approved regimen sofosbuvir (NS5B inhibitor) plus ribavirin in patients infected with HCV genotypes 1-4 co-infected with HIV. They confirm the pan-genotypic potential of sofosbuvir (SVR 12 weeks: 84.8%), offering HIV co-infected patients a useful interferon-free option. The fourth trial published in today’s issue goes a step further and assesses whether the addition of a third direct-acting antiviral drug to an interferon-free, ribavirin-free combination (sofosbuvir and ledipasvir) would allow shorter treatment duration—an important factor for a patient population in which treatment compliance and adherence can be an issue.

These trials are important because they offer new effective treatment options for HCV infection. “An opportunity now exists to almost eliminate this infection from the UK,” wrote Roger Williams and colleagues in The Lancet Commission on Addressing liver disease in the UK. Highly effective new antiviral drugs not only can cure those treated but also can reduce transmission of HCV and therefore its prevalence. The Commission estimated that with these new antiviral drugs, we could contemplate the eradication of infections from chronic hepatitis C virus in the UK by 2030.” Indeed, modelling studies for England showed that increasing diagnostic and number of people treated by 2.7 times would result in a 95% reduction in the prevalence of HCV infection, an 80% reduction in hepatocellular carcinoma, and avert 15,000 deaths by 2030.

While new drugs offer new opportunities, new challenges also arise. Scaling up treatment—in any country—will face important cost issues. But the high costs of these new medicines, which should be robustly scrutinised and, where appropriate, challenged, must not inhibit a careful and comprehensive analysis of the broader benefits they might bring. For example, as Melanie Calvert and colleagues argue this week, patient-reported outcomes offer the opportunity to have the patient’s voice more forcefully heard in health policy decision making. The self-reported benefits to patients from these new anti-HCV regimens might prove to be substantial. And the financial returns from reduced health-care costs and higher economic activity might easily outweigh the expense of the medicines themselves. This kind of broader cost-effectiveness work needs to be urgently completed.

Next month, The Lancet Infectious Diseases is hosting its inaugural Viral Hepatitis Summit in Shanghai (April 10–12). We look forward to this meeting addressing the increasingly urgent need for a global plan to eliminate hepatitis C. With no vaccine in sight, if we are truly to contemplate elimination of hepatitis C by 2030, ensuring that treatments reach marginalised groups and are accessible to all those living with HCV will be crucial. —The Lancet
Hepatitis C: only a step away from elimination?

Globally, an estimated 185 million people are infected with hepatitis C virus (HCV). Acute HCV infections are usually asymptomatic. However, about 75% of patients develop chronic infection, which can lead to liver cirrhosis and hepatocellular carcinoma. 700,000 deaths worldwide could be attributed to HCV in 2013. While most people affected live in low-income and middle-income countries in Asia, Africa, and the Middle East, in the UK an estimated 200,000 individuals are infected with HCV, and annual deaths from HCV have quadrupled since 1996. These figures are appalling, surely. But the extraordinary recent developments in treatment for hepatitis C offer substantial grounds for optimism. A series of new drugs—more effective in viral clearance with fewer side effects—are changing the landscape for hepatitis C.

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Can All Patients With HCV Infection Be Cured?

- Achievable at individual patient level if every patient could be treated

- 4 key obstacles to curing HCV globally
  - Screening and diagnosis
  - Access to care
  - Simplicity of therapy
  - Affordability

# Barriers to Treatment That Persist

<table>
<thead>
<tr>
<th>Treatment Barriers</th>
<th>Overcoming Barriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotyping</td>
<td>Single regimen and duration for all GT</td>
</tr>
<tr>
<td>HCV RNA</td>
<td>No RGT; minimal risk of viral breakthrough</td>
</tr>
<tr>
<td>Safety monitoring labs</td>
<td>RBV-free regimen; no toxicity</td>
</tr>
<tr>
<td>Availability of specialists</td>
<td>Community healthcare providers able to deliver simple, safe treatment</td>
</tr>
<tr>
<td>Economic burden</td>
<td>Access programs</td>
</tr>
</tbody>
</table>

Courtesy of Dr. J McHutchinson
Better HCV Treatments Will Allow Simplified Diagnostic Pathway

Present

- **Diagnosis**
  - HCV antibody (EIA/RDT)
  - HCV Antigen (NAT/Ag)

- **Treatment assessment**
  - HCV Viral load
  - HCV genotype
  - Fibrosis assessment

- **Treatment monitoring**
  - HCV Viral load
  - Toxicity monitoring

- **Post-Rx**
  - HCV Viral load

Future

- **HCV Antigen RDT**

- **HCV Antigen RDT**

- **HCV Antigen RDT**

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Adapted from UNITAID Hepatitis C Medicines and Diagnostics in the Context of HIV/HCV Co-Infection. 2013

EIA: enzyme immunoassay; NAT: nucleic acid test; RDT: rapid diagnostic test
Simplification of antiviral hepatitis C virus therapy to support expanded access in resource-limited settings

Nathan Ford¹, Tracy Swan², Peter Beyer³, Gottfried Hirnschall¹, Philippa Easterbrook³, Stefan Wiktor¹,*

¹Department of HIV/AIDS, World Health Organization, Geneva, Switzerland; ²Treatment Action Group, New York, USA; ³Department of Essential Medicines and Health Products, World Health Organization, Geneva, Switzerland
### Table 1. Key steps to facilitate scale-up access to DAAs in low- and middle-income settings.

<table>
<thead>
<tr>
<th>Key steps for allowing delivery of HCV treatment at scale</th>
<th>Potential approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simplified screening for treatment</td>
<td>• Combined test (e.g. antibody and antigen) for one-step diagnosis</td>
</tr>
<tr>
<td>Standardization of treatment regimens</td>
<td>• Definition of limited number of preferred regimens for resource-limited settings</td>
</tr>
<tr>
<td></td>
<td>- Key characteristics:</td>
</tr>
<tr>
<td></td>
<td>- oral</td>
</tr>
<tr>
<td></td>
<td>- pan-genotypic</td>
</tr>
<tr>
<td></td>
<td>- interferon-free</td>
</tr>
<tr>
<td></td>
<td>- fixed-dose combination</td>
</tr>
<tr>
<td>Simplified laboratory monitoring</td>
<td>• Definition of a minimal package of diagnostic and monitoring tests</td>
</tr>
<tr>
<td>Service delivery</td>
<td>• Delegation of key tasks to lesser trained health staff</td>
</tr>
<tr>
<td></td>
<td>• Decentralization of care to lower level health facilities</td>
</tr>
<tr>
<td>Patient self-management</td>
<td>• Promotion of patient-centred treatment literacy and adherence support</td>
</tr>
<tr>
<td>Access to affordable medicines</td>
<td>• Voluntary licensing</td>
</tr>
<tr>
<td></td>
<td>• Compulsory licensing</td>
</tr>
<tr>
<td></td>
<td>• Patent oppositions</td>
</tr>
<tr>
<td></td>
<td>• Increased price transparency</td>
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<tr>
<td></td>
<td>• Patent sharing arrangements</td>
</tr>
<tr>
<td></td>
<td>• Bulk procurement</td>
</tr>
</tbody>
</table>
“it always seems impossible, until its done” (N. Mandela)