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What should a new pharmaceutical consensus for low cost/generic provision of antiretrovirals look like?

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What does a pharmacological consensus mean?

- A consensus among pharma companies?
- A consensus among all stakeholders, including patients, providers, payers (insurance companies, governments, donors)?
- About low-, middle- or high income countries, or all of these?

Let us assume

- That we are speaking about a consensus among all stakeholders, including patients, providers, and payers.
- Which concerns low-, middle- and high income countries.

A little history (1)

- 1996: introduction of HAART* in high income countries (HICs).

- Virtually no movement to bring this life-saving intervention to hardest hit low-income countries:
  - too expensive;
  - too complex;
  - “prevention” more important/cost-effective than treatment.

* Now often called cART, but dual therapy is also cART, so an even sillier name than HAART.

A little history (2)

- International AIDS Conference held in Durban South Africa.

- Preceded by an agreement between UNAIDS and 5 large pharmaceutical companies to start providing antiretrovirals at greatly reduced prices to poor countries Accelerating Access Initiative: AAI.

A little history (3)

- The AAI was a start, which allowed for demonstration projects.

- Since very little external funding for treatment was available at the time, it did, however, not result in significant national scale-up programs in sub-Saharan Africa.*

*Botswana was the exception, but, even in this middle-income country most of the funding was provided by external donors (Merck and the Bill and Melinda Gates Foundation).

A little history (4)

- Moreover, until WHO launched the **3by5 initiative** it did not send a clear message to countries regarding the need to scale up.

- Fortunately, the launch of 3by5 more or less coincided with or was followed shortly thereafter with the launch of **sizable funding mechanisms**:
  - the World Bank's Multicountry AIDS Program (MAP);
  - the Global Fund to Fight AIDS, TB and Malaria (GFATM); and,
  - the US President's Emergency Plan for AIDS Relief.

A little history (5)

- Followed by increasing involvement of generic manufacturers (mainly from India).
- Ever decreasing prices due to negotiations and volume commitments by the Clinton HIV/aids Initiative (now Clinton Health Access Initiative, CHAI).
- Middle income countries (like Brazil and Thailand), with the ability to produce generics could use the threat of domestic production to lower the price of originator drugs.
- TRIPS also allowed for compulsory licensing.

A little history (6)

- After initial resistance by originator companies to generic competition, more and more, but not all, companies decided not to uphold patents in the poorest and hardest hit countries, but to give licenses to generic companies to produce “their” antiretrovirals for these markets.

- Some of them have even have joined the Medicines Patent Pool (MPP).

Medicines Patent Pool (MPP)

- Created in 2010 in order to:
  - Cause a reduction in the price of HIV medicines for those living in low- and middle income countries;
  - To encourage the development of better adapted HIV medicines.

- Financed by UNITAID.

- Has come to license agreements with Gilead Sciences, NIH, ViiV Healthcare, Roche and Bristol-Myers Squibb.

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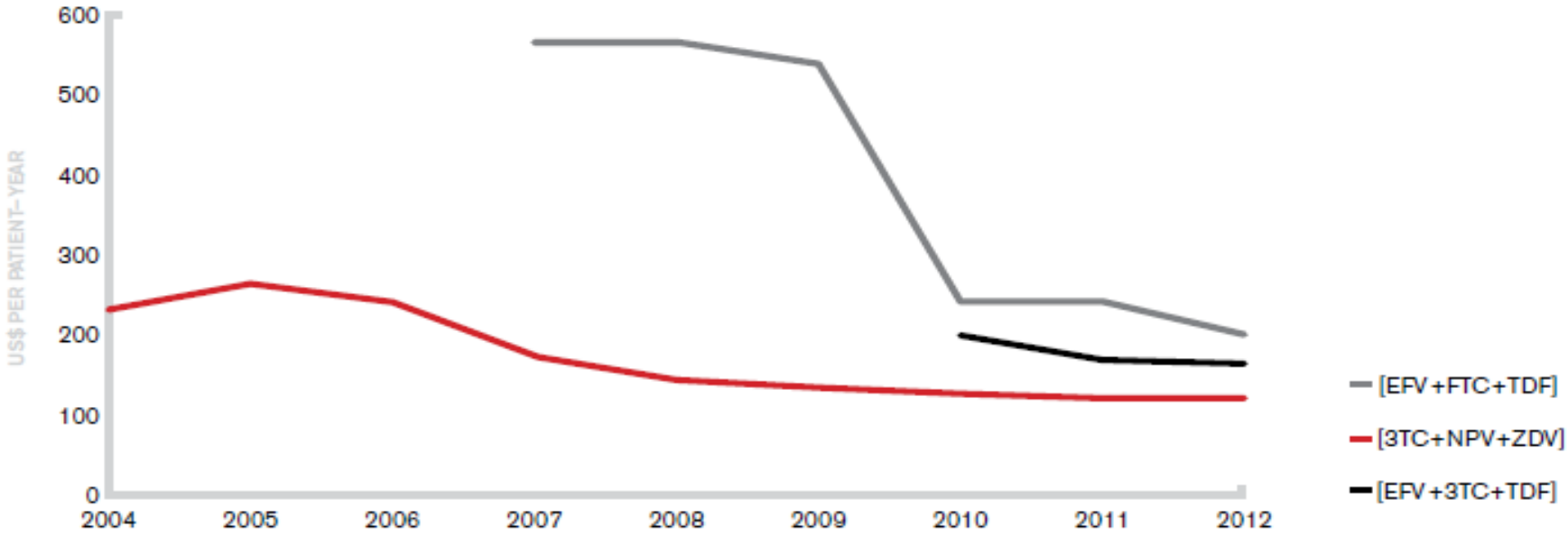
Median prices of WHO-recommended first-line regimens in low- and middle-income countries, 2004–2012 (US$ per patient-year)



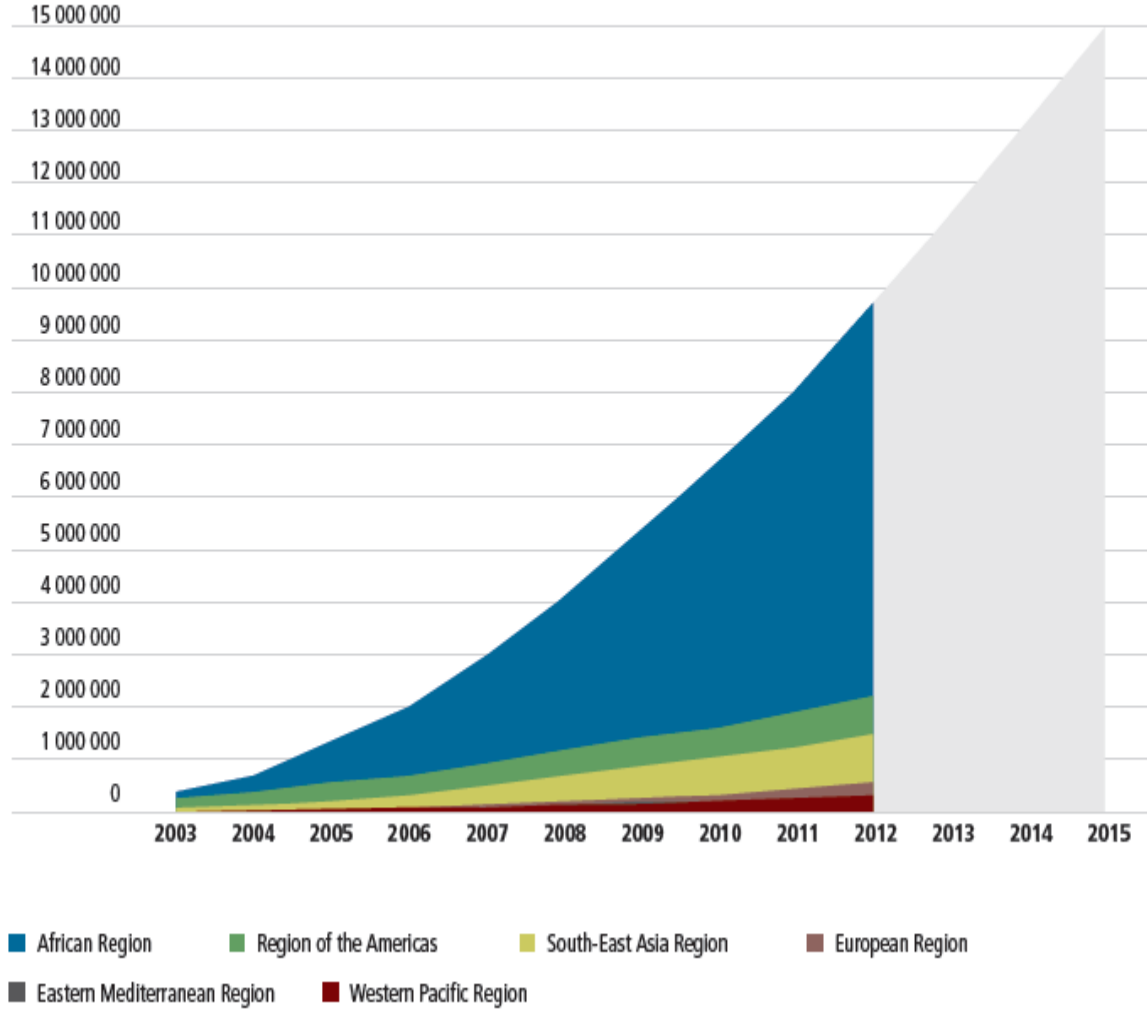
The Strategic Use of Antiretrovirals to Help End the HIV Epidemic, WHO 2012

Another critical element of the scale-up

- Regulatory framework
  - WHO prequalification*
  - FDA expedited review provisions (PEPFAR)

*'t Hoen EF, et al. A quiet revolution in global public health: The World Health Organization's Prequalification of Medicines Programme. *J Public Health Pol*icy 2014: epub.

Fig. 1. Actual and projected numbers of people receiving antiretroviral therapy in low-and middle-income countries, and by WHO Region, 2003–2015



Source: 2013 Global AIDS Response Progress Reporting (WHO/UNICEF/UNAIDS).

Are prices paid for ARV's in low income countries "sustainable"? (1)

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- In 2005, the ration of formulation cost over the cost of API was over 1.33 ("commercially viable") for 4 out of 5 adult formulations.

- By 2012, the proportion of adult formulations categorized as commercially viable had decreased to 2 out of 11.

- Nevertheless, the authors conclude: "further price reduction for WHO preferred regimens is likely still possible..".

  - Perriëns JH, et al. Antiviral Therapy: in press.

Are prices paid for ARV's in low income countries "sustaianable"? (2)

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- "While recent price decreases indicate there is still space for price reduction, our estimate that gross profit margin on sales decreased by 6 to 7% between 2010 and 2012 lends credibility to assertions by generic manufacturers that the ARV market in low income countries is under considerable pressure."

  - Nakakeeto ON & Elliott BV. Globalization and Health 2013,9:6.

Patent Expiry dates for HIV drugs

The original 20 year patents for most key antiretrovirals have already expired, or will expire in the next 3-4 years.

However there are patents on single tablet regimens, which will remain in place until 2026 any beyond

This has serious cost implications for key middle income countries with large HIV epidemics

e.g. Eastern Europe / Russia

Thailand / SE Asia

South America

Patent Expiry dates for HIV drugs

2012: ZDV, 3TC, d4T, ddI, SQV, NVP – generic

2013: ritonavir, efavirenz, ZDV/3TC – generic

2016: abacavir, LPV/r (soft-gel)

2017: atazanavir, tenofovir, darunavir

2019: etravirine, ABC/3TC (Kivexa)

2024: TDF/FTC (Truvada)

2025: raltegravir

2026: TDF/FTC/EFV (Atripla), TDF/FTC/RPV (Complera), dolutegravir

Ref: Medecins Sans Frontieres 2013: Untangling the web of ARV price reductions

The choice for middle-income countries: – pill counts versus price?

Single patented pill
Higher cost

TDF/FTC/EFV
TDF/FTC/RPV
TDF/FTC/ETG/c
ABC/3TC/DTG

Three generic pills
Lower cost

Generic TDF, ZDV, ABC

Generic 3TC

Generic NVP, EFV (400)

The generic version may be better tolerated, if the EFV dose is lower

Sources: BNF 2013, generic company prices

How important is pill burden? (1)

- In an observational cohort study of 118 **homeless or unstably housed** individuals in San Francisco, taking a single-tablet regimen (STR) was associated with greater adherence and viral suppression compared with a multitablet regimen (MTR).

*Bangsberg, et al. aids 2010;24:2835-40.

How important is pill burden? (2)

- One recently published study analyzing a commercial US insurance claims database found that:
  - a STR was associated with increased adherence, and,
  - the increased likelihood of complete adherence was associated with a 25% decrease in the rate of hospitalization.*

*Sax PE, et al. PLoS ONE 7:e31591.

How important is pill burden? (3)

- Study in US Medicaid population found that:
  - patients using a STR were significantly more likely to be highly adherent; and,
  - had a lower risk of hospitalization, and other healthcare utilization and costs.*

*Cohen CJ, et al. BMJ Open 2013.

How important is pill burden? (4)

- Study in women enrolled in the US Women's Interagency HIV Study (WIHS) found that:

  - use of a STR was significantly associated with increased adherence and virologic suppression. more likely to be highly adherent.*
    (**25% had a history of injection drug use**)

*Hanna DB, et al. J Acquir Immune Def Syndr 2014;65:587-96.

But.....

- If all eligible US patients would start with or switch to a generic-based three pill regimen of TDF (non-generic!), 3TC and EFZ, instead of starting or remaining on STR of TDF/FTC/EFZ, estimated first year savings would be $920 million.

*Walensky RP, et al. Ann Intern Med 2013;158:84-92.

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PLOS ONE

Comparative Efficacy of Lamivudine and Emtricitabine: A Systematic Review and Meta-Analysis of Randomized Trials

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Abstract

Introduction: Lamivudine and emtricitabine are considered equivalent by several guidelines, but evidence of comparable efficacy is conflicting.

Methods: We searched two databases up to June 30 2013 to identify randomized and quasi-randomized trials in which lamivudine and emtricitabine were used as part of combination antiretroviral therapy for treatment-naïve or experienced HIV-positive adult patients. We only included trials where partner drugs in the regimen were identical or could be considered to be comparable. We allowed for comparisons between tenofovir and abacavir provided the study population did not begin treatment with a viral load >100,000 copies/ml.

Results: 12 trials contributed 15 different randomized comparisons providing data on 2251 patients receiving lamivudine and 2662 patients receiving emtricitabine. Treatment success was not significantly different in any of the 12 trials. In the three trials that directly compared lamivudine and emtricitabine, the relative risk for achieving treatment success was non-significant (RR 1.03 95%CI 0.96-1.10). For all trials combined, the pooled relative risk for treatment success was not significantly different (RR 1.00, 95%CI 0.97–1.02). No heterogeneity was observed (I^2 =0). Similarly, there was no difference in the pooled relative risk for treatment failure (RR 1.08, 95%CI 0.94–1.22, I^2 = 3.4%).

Conclusions: The findings of this systematic review suggest that lamivudine and emtricitabine are clinically equivalent.

Citation: Ford N, Shubber Z, Hill A, Vitoria M, Doherty M, et al. (2013) Comparative Efficacy of Lamivudine and Emtricitabine: A Systematic Review and Meta-Analysis of Randomized Trials. PLoS ONE 8(11): e79981. doi:10.1371/journal.pone.0079981

Editor: Mark Wainberg, McGill University AIDS Centre, Canada

Received August 18, 2013; **Accepted** October 5, 2013; **Published** November 11, 2013

Funding: This work was supported by funds from the Bill and Melinda Gates Foundation. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

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Introduction

Lamivudine and emtricitabine are both widely used as a core component of the dual nucleoside reverse transcriptase inhibitor backbone in all currently preferred first-line antiretroviral combinations therapies The chemical structure of these two nucleoside analogues is very similar[1,2]; both are prodrugs requiring intracellular phosphorylation and both are active against HIV-1, HIV-2 and hepatitis B virus.

The latest antiretroviral treatment guidelines of the US Department of Health and Human Services [3] and the World Health Organization[4] consider lamivudine and emtricitabine to be equivalent and interchangeable from a clinical and programmatic perspective. However, inferior virological efficacy of lamivudine has been suggested based on limited data from early in-vitro studies[5,6] and this presumption of inferiority has been applied to recent cost-effectiveness analyses [7]. There is therefore uncertainly regarding the clinical comparability of these two drugs.

In order to support recommendations for future guidance for first-line antiretroviral therapy, we conducted this systematic review of available data from randomized trials to assess the comparative efficacy of these two antiretroviral drugs.

Methods

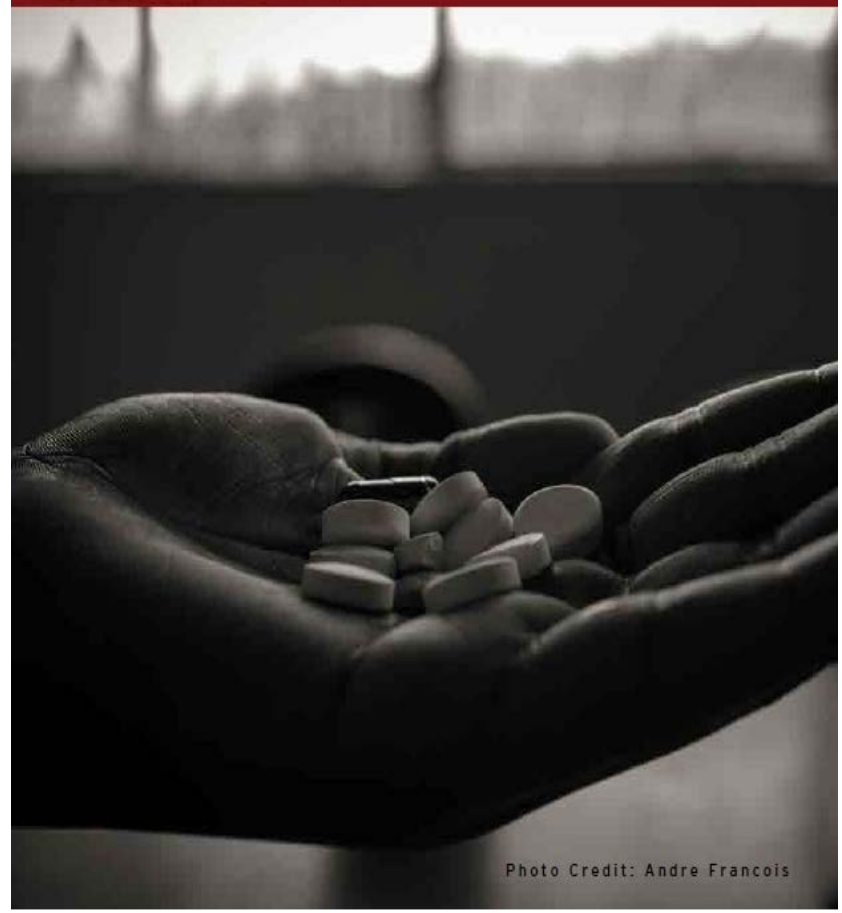
This systematic review was conducted according to the according to the criteria of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses group [8].

Search strategy and study selection

Using a pre-defined protocol, we sought randomized and quasi-randomized trials in which lamivudine and emtricitabine were used as part of combination antiretroviral therapy for treatment-naive or treatment-experienced HIV-positive adult patients. Our search strategy was conducted in 2 stages. In the first stage, we screened separately in Medline (via PubMed) from inception to March 31 2013 for all trials including lamivudine or emtricitabine in one arm in an attempt to identify trials that could be compared indirectly through a network meta-analysis. In the second stage, we searched Medline, Embase, and the Cochrane Database of

STOP STOCKOUTS

Stock Outs in South Africa
A National Crisis



MEDECINS SANS FRONTIERES

+SECTION27
catalysts for social justice

RUDASA

TAC
TREATMENT ACTION CAMPAIGN

Rural Health Advocacy Project

In conclusion

Critical “enablers” of the antiretroviral scale up:

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- Price reductions of ARVs: generics
- Funding:
  - World Bank MAP
  - GFATM
  - PEPFAR
- Target setting by WHO (3by5)
- Patient activism (TAC, etc.)
- Regulatory framework
  - WHO prequalification
  - FDA

Pressing questions

- Will generic manufacturers bow out of producing exceedingly cheap antiretrovirals for resource-poor settings?

- Is 3TC really equivant to FTC in settings with drug supply interruptions?
  - Do we need a RCT comparing STRs of TDF/FTC/EFC and TDF/3TC/EFZ in sub-Saharan Africa?

- Will high income countries move away from SRTs to save costs and what impact will this have on adherence?

PHARMACEUTICALS

Advocates Protest the Cost of a Hepatitis C Cure

For disease advocates, the U.S. Food and Drug Administration's 6 December approval of what promises to become a blockbuster drug against the hepatitis C virus (HCV) was bittersweet news. Sofosbuvir, made by Gilead Sciences of Foster City, California, works better than anything on the market: It's effective against most HCV variants and will help rid the body of this liver-damaging virus more quickly and safely than existing drugs. What rankles advocates is its price—each pill costs $1000, and the drug must be used for at least 12 weeks—which will put it out of reach of most of the more than 100 million people in resource-limited countries who need it. "It doesn't matter how great these drugs are if no one can have them," says Tracy Swan, who works with the Treatment Action Group, a New York City nonprofit whose members successfully battled big pharma as leading AIDS activists in ACT UP.

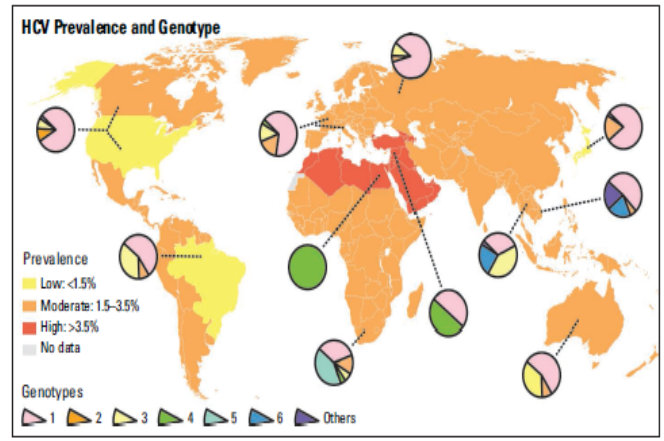
In an unusual move, Swan and other HCV advocates have been imploring Gilead to offer a lower price to cash-strapped countries right from the start. They want to avoid a repeat of what happened during the early days of the AIDS epidemic, when it took years—and many protests and lawsuits—before the poor had access to lifesaving antiretroviral drugs. "We want the drug now—not in 15 years," says Isabelle Meyer-Andrieux, a clinician based in Geneva, Switzerland, who works for the Campaign for Access to Essential Medicines run by Doctors Without Borders (Médecins Sans Frontières [MSF]). "We are really convinced that this drug can revolutionize the way we treat HCV in low- and middle-income countries."

Meyer-Andrieux says that Gilead seems receptive to differential pricing, a strategy the company uses for its anti-HIV drugs. Gregg Alton, Gilead's executive vice president for corporate and medical affairs, wrote in an e-mail to *Science* that the company hopes "to develop an appropriate access and pricing strategy" and "greatly values" input from advocates. "Providing treatment in resource-limited settings presents complex challenges and we understand the concerns that have been raised," he wrote.

HCV, which can cause life-threatening cirrhosis and liver cancer, infects an estimated 130 million to 185 million people—and 90% of them live in poorer countries (see map). It's mainly transmitted through contaminated blood transfusions or syringes shared by injecting drug users, but sexual transmission can occur, too. There are six main viral variants, called genotypes, which respond differently to treatments. New drugs are desperately needed.

Until 2011, the only treatment was an unpopular 48-week regimen that combined injections of interferon with ribavirin pills, which boosted the immune system and had some nonspecific antiviral effect but didn't directly attack HCV. The treatment often had severe side effects and cured fewer than 50% of those with genotype 1, which infects about 70% of the estimated 3 million people in the United States with hepatitis C. In the past 3 years, three drugs have come to market that directly attack HCV and reduce treatment regimens to 12 to 28 weeks, but they are approved only to treat genotype 1, some have serious side effects, and cure rates are, at best, 80%.

Gilead's sofosbuvir cripples an HCV enzyme, polymerase, that the virus needs to copy itself. The drug cures roughly 90% of genotype 1, 2, and 4 infections in 12 weeks with relatively minor side effects, when given with ribavirin and, for genotypes 1 and 4, interferon injections. It's also approved for use in combination with ribavirin for genotype 3, although efficacy is slightly lower and treatment takes 24 weeks.



The drug's performance in early studies led Gilead in January 2012 to pay a staggering $11.2 billion to purchase the small company that first made it. But Meyer-Andrieux argues that the full-price sales of the drug in wealthy countries will offer the company ample profit. "They don't have to treat so many patients to reimburse the $11 billion," she says. A 20 November investor report from Credit Suisse bank, subtitled "The HCV Revolution," suggests sofosbuvir's sales in wealthy countries in 2014 alone could total $3 billion.

"The drugs are extremely cheap to make," contends Andrew Hill, a pharmacologist at the University of Liverpool in the United Kingdom. Based on the raw ingredients, the steps in the chemical synthesis, and molecular similarities to anti-HIV drugs, Hill and his colleagues concluded that it costs $68 to $136 to manufacture enough sofosbuvir to treat a person for 12 weeks. MSF suggests that diagnosing and curing an HCV infection should cost developing countries no more than $500.

Hoping to pave the way for an inexpensive generic version of sofosbuvir, another nonprofit is challenging Gilead over its Indian

CREDIT: ADAPTED FROM MOHD HANAFIAH ET AL., *HEPATOLOGY* 57 (APRIL 2013); NIZAR N. ZEIN, *CLINICAL MICROBIOLOGY REVIEWS* 13 (APRIL 2000)

Acknowledgement

- Andrew Hill