

94% SVR With Parallel Imported Generic Direct Acting Antiviral Treatment for Hepatitis C

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Disclaimer

- Many medications discussed annually at EASL do not have registration in any jurisdiction (ie GS-9857, ABT-493, ABT-530, MK-3682)
- The medications used in generics trials differ in that while they may be registered for use in certain jurisdictions, they are not registered in many jurisdictions, including the Netherlands
- In the Netherlands personal medication importation is not permitted, so while elements of the content of this presentation are applicable in a majority of countries, they are not universally applicable, and particularly not applicable to the Netherlands
- We strongly recommend readers make their own enquires with respect to applicable local rules and regulations

Disclosures

- Financial Support: None - the authors of this study all paid their own costs
- Conflicts Of Interest:
 - James Freeman has received travel support from European Egyptian Pharmaceutical Industries and Beacon Pharma
 - Andrew Hill has received consultancy payments from Merck, Teva and Janssen in the past 12 months
 - Greg Jefferys treated himself with generic HCV medications and provides information and help to other patients seeking access to treatment
 - Giten Khwairakpam has no conflicts of interest to declare
 - Julia Dragunova has no conflicts of interest to declare
 - Sergey Golovin has no conflicts of interest to declare
 - James Wang has no conflicts of interest to declare
 - Vicky Houghton-Price has no conflicts of interest to declare
 - Rachel Smith has no conflicts of interest to declare
 - Roxanna Korologou-Linden has no conflicts of interest to declare
 - Dr John Freeman has no conflicts of interest to declare

A Global Tragedy

- In a breakthrough that rivals the invention of penicillin, drugs which cure Hepatitis C (HCV) have reached the market, and yet
- Every 45 seconds another patient dies of Hepatitis C
- So it remains one of the greatest tragedies of modern times that these life saving drugs are not being deployed on a mass scale
- **The deployment problem is price**
 - It's suggested that Daclatasvir is worth the same as Diamonds

5g of Diamonds

25 1-carat @ \$2000 each

Cost = \$50,000



5g of Daclatasvir

12 weeks @ 60mg/day

Cost = \$50,000 (UK price)



Hep C CURE

ENTRY FEE

\$84,000

Generic Hep C
Cure

\$1,500



Background

- Unaffordable prices prevent patient access
- Generic DAAs are being mass produced at low cost
 - 1% of the current US retail price¹, and
 - Sofosbuvir, ledipasvir, daclatasvir, velpatasvir and ribavirin are all currently available as generics
- Many, but not all, countries allow some form of personal medication importation
 - Under the laws of Australia², the UK³, and many other countries, individuals have the right to import a three month supply of medication, for their personal use.

1. [Hill A. Minimum Costs for Producing Hepatitis C Direct-Acting Antivirals. Clin Inf Dis. 2014](#)

2. <https://www.tga.gov.au/personal-importation-scheme>

3. <https://www.gov.uk/government/organisations/hm-revenue-customs>

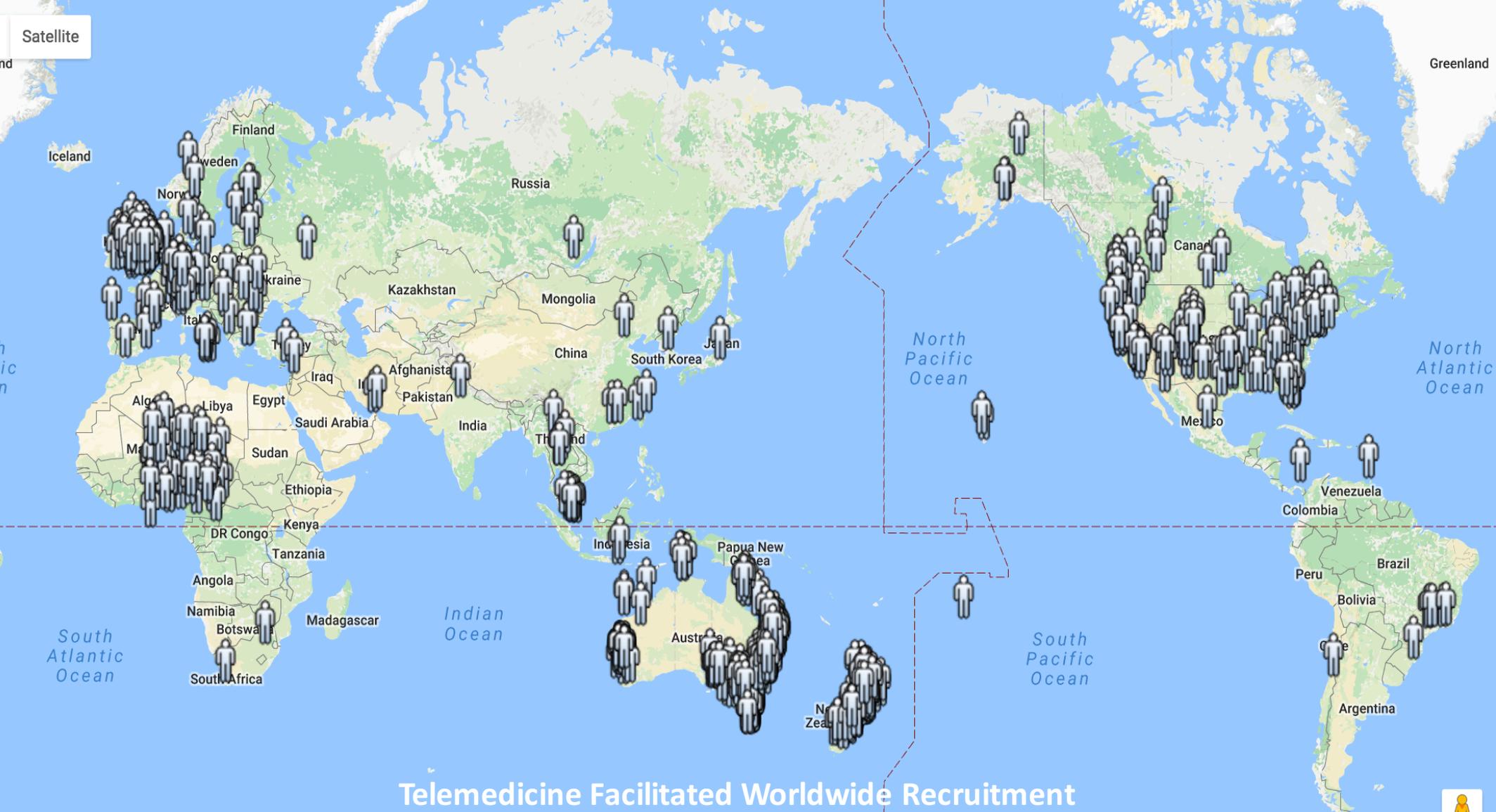
The Legal Basis Of Personal Importation

- Patents provision monopoly rights, however...
- Article 60 of TRIPS - De Minimis Imports – provisions a personal importation right
 - *Article 60: Members may exclude from the application of the above provisions small quantities of goods of a non-commercial nature contained in travellers' personal luggage or sent in small consignments*
- We can observe patients making self importations
 - The question for us, as the medical profession is how we respond
 - Should we oppose it, should we support it, should we ignore it?
 - I made a decision to prioritize my patients

Methods – REDEMPTION-1

- Generic DAAs were evaluated for quality
 - Tested with HPLC, NMR and Mass Spectrometry
- 448 consecutive patients enrolled
- Underwent routine assessment
 - Baseline, on treatment, and post treatment for SVR4, SVR12 and SVR24
- Objective was to answer two key clinical questions:
 - Do generics work?
 - Are they safe?

Satellite

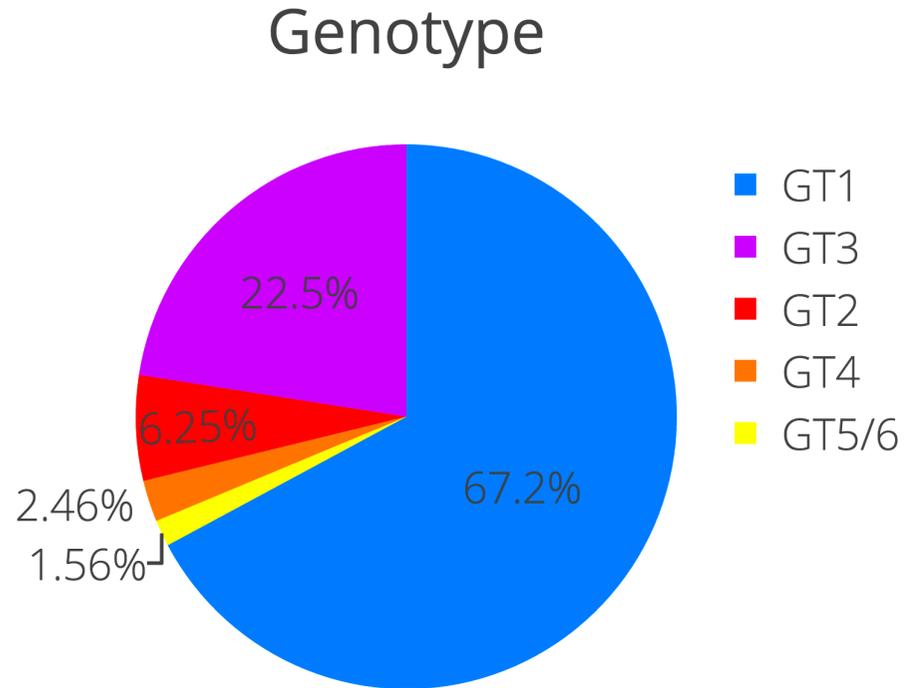


Telemedicine Facilitated Worldwide Recruitment

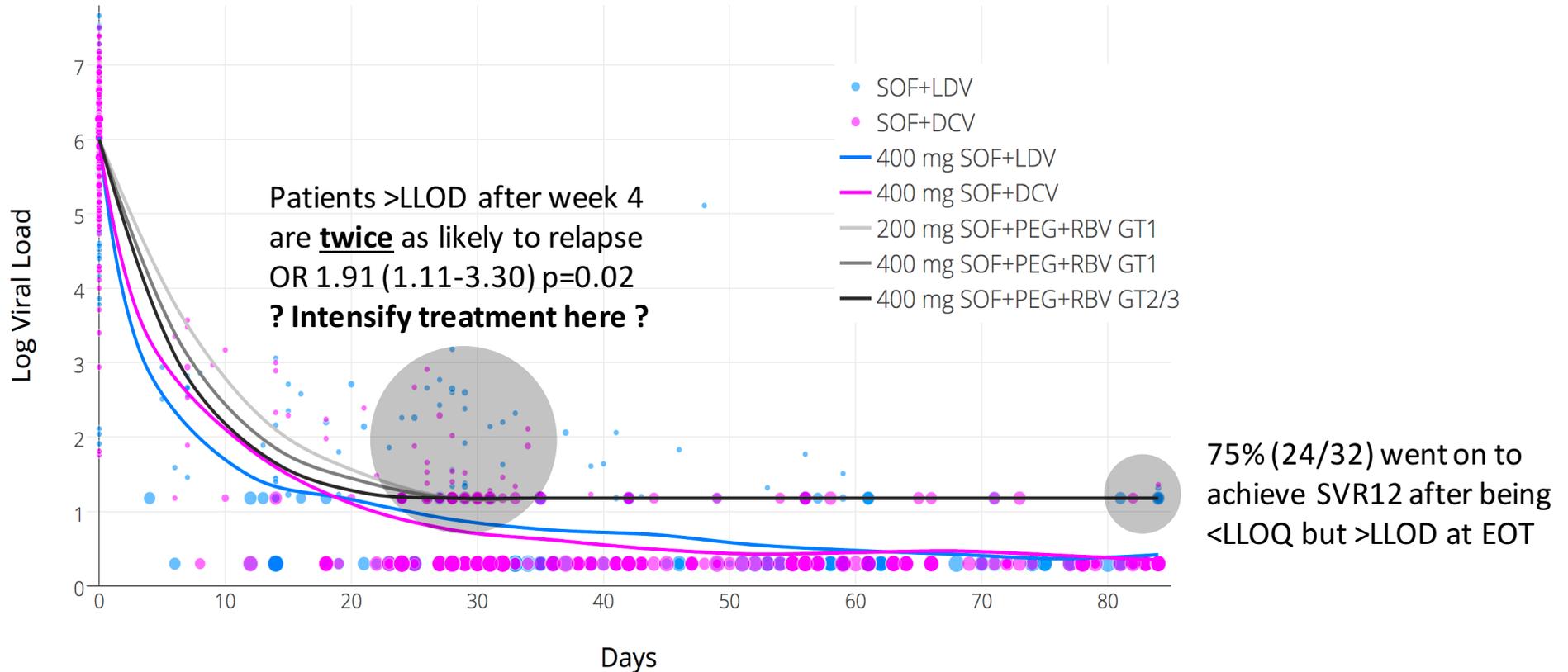


Baseline Characteristics

n	448
SOF+RBV	0.9% (4/448)
SOF+LDV	45.8% (205/448)
SOF+LDV+RBV	4.7% (21/448)
SOF+DCV	42.6% (191/448)
SOF+DCV+RBV	6.0% (27/448)
Naïve	57.6%
Cirrhosis	28.0%
Male	57.4%
Mean Age	55.4 years
Mean HCV RNA	6.47 log IU/ml 2943565 IU/ml



Viral Response vs SOF+PEG+RBV



SOF+PEG+RBV kinetics data source:

[http://www.thelancet.com/journals/laninf/article/PIIS1473-3099\(13\)70033-1/fulltext](http://www.thelancet.com/journals/laninf/article/PIIS1473-3099(13)70033-1/fulltext)

Negative Predictors of SVR

Factor	Relapse	Cohort	Odds Ratio (95% CI)	p
Cirrhosis	54%	28%	1.92 (1.16-3.21)	0.01
Detectable after day 24	44%	22%	1.91 (1.11-3.30)	0.02
GT3	38%	23%	1.69 (0.95-2.98)	0.07
Male	80%	57%	1.39 (0.89-2.17)	0.14
Ribavirin	12%	12%	1.03 (0.42-2.5)	0.94
Naive	52%	58%	0.90 (0.54-1.48)	0.69
Female	20%	42%	0.47 (0.23-0.95)	0.03

The significance of detectable at 4 weeks (OR 2.5) was also found in the study **Real World Effectiveness of Ledipasvir/Sofosbuvir in 4365 Treatment-Naïve Genotype 1 Hepatitis C Infected Patients¹**

1. https://www.researchgate.net/publication/301671429_Real_World_Effectiveness_of_LedipasvirSofosbuvir_in_4365_Treatment-Naive_Genotype_1_Hepatitis_C_Infected_Patients

Three Reasons This Is Important

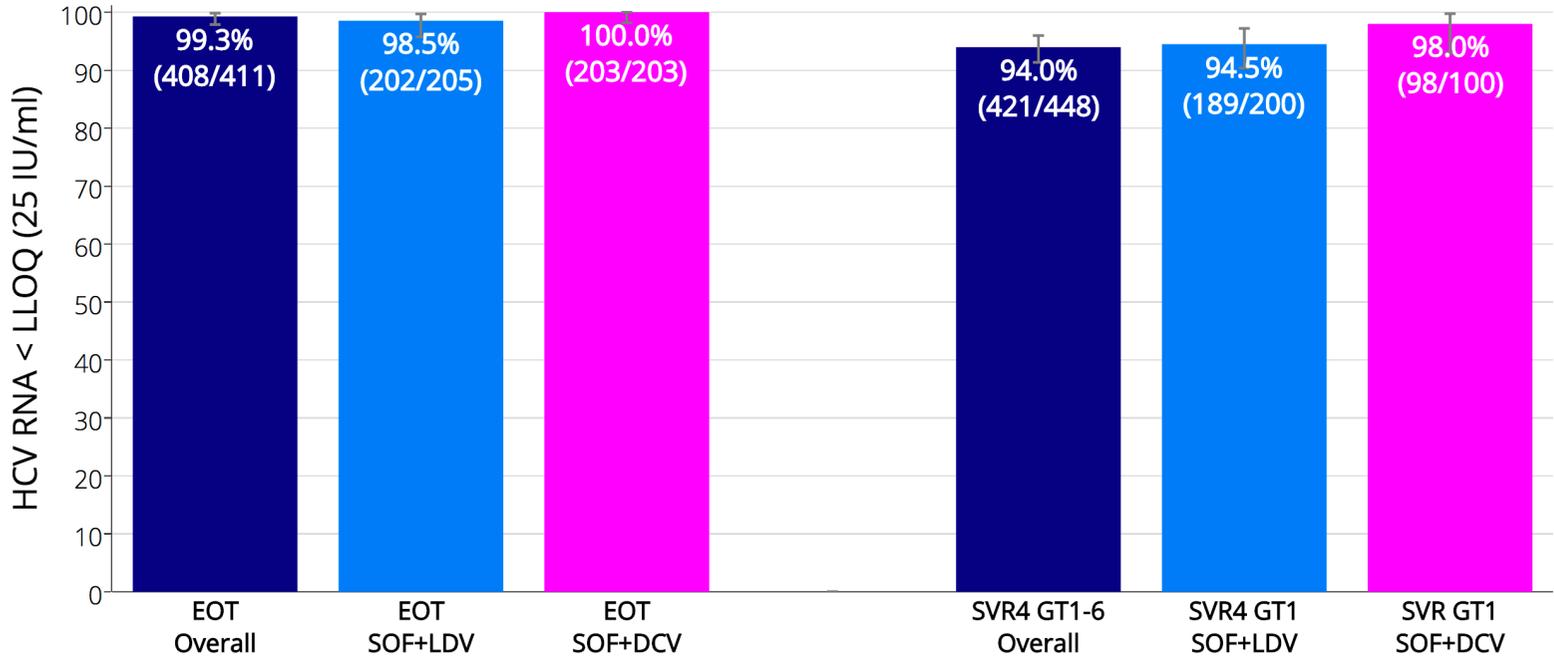
1. If we can cheaply and easily identify a group of patients at much higher risk of failure, at a time when we can do something about it, then we can intensify treatment
 - C-SWIFT Zepatier + Sofosbuvir¹ – Salvage rate 100% (23/23) with 80% baseline RAVs
 - QUARTZ-1 Viekira + Sofosbuvir¹ – Salvage rate 95% (21/22)
2. It is more cost efficient to piggyback on top of the planned treatment rather than retreat
 - We can get more cures per dollar spent
3. Finally, with HIV, having a viral load on treatment means the replicating virions are, by definition, at least partially resistant to the current regimen
 - They are also a single mutation away from multidrug resistance

1. <http://www.infohep.org/Treatment-intensification-with-sofosbuvir-permits-cure-after-failure-of-previous-HCV-treatment/page/3014990/>

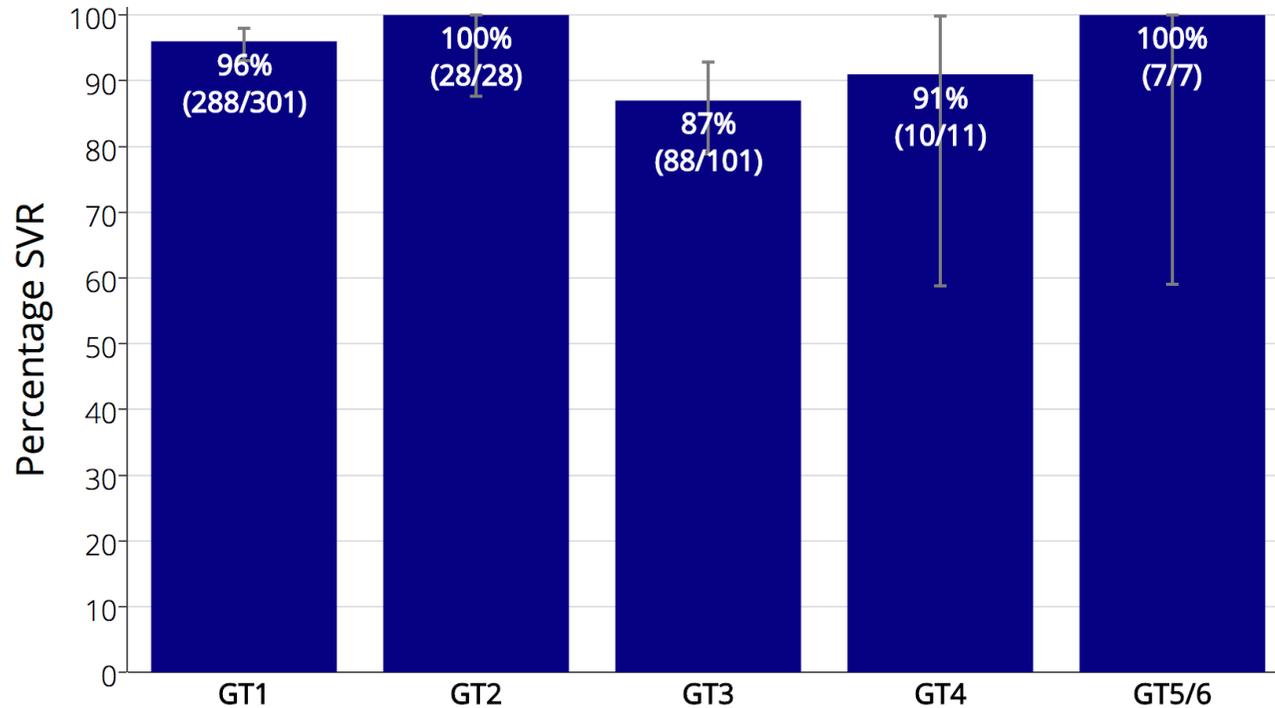
Patient Safety

- No new or unknown side effects were reported
 - Headache, fatigue and insomnia were the most common
- 3 patients with compensated cirrhosis de/re-compensated
 - All shortly after treatment initiation and all re-compensated and continued
- 4 patients who enrolled died - all from HCC
 - 1 prior to treatment commencement
 - 2 withdrew early in treatment and entered palliative care
 - 1 prior to SVR4
- 1 patient reactivated their Hepatitis B
 - They had declined prophylaxis and responded well to Entecavir

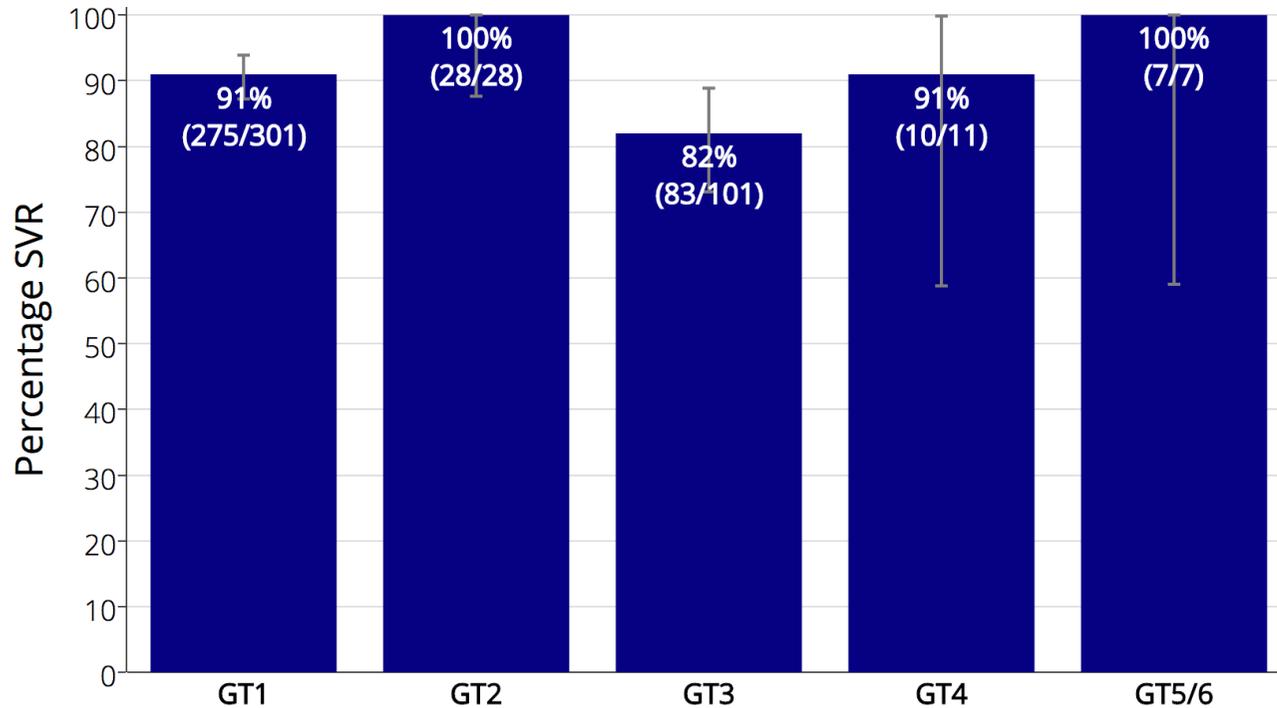
HCV RNA < LLOQ at EOT and SVR4



SVR4 Results by Genotype



SVR12 Results by Genotype



With Over 99% Follow Up of 448 Consecutive Patients Taking Generics.....

HCV RNA <25 IU/ml

RVR:	85.7%	(198/231)	CI	80.5%	-	90.0%
EOT:	99.3%	(408/411)	CI	97.9%	-	99.8%
SVR4:	94.0%	(421/448)	CI	91.3%	-	96.0%
SVR12:	90.0%	(403/448)	CI	86.8%	-	92.6%
LTFUP:	0.4%	(2/448)				

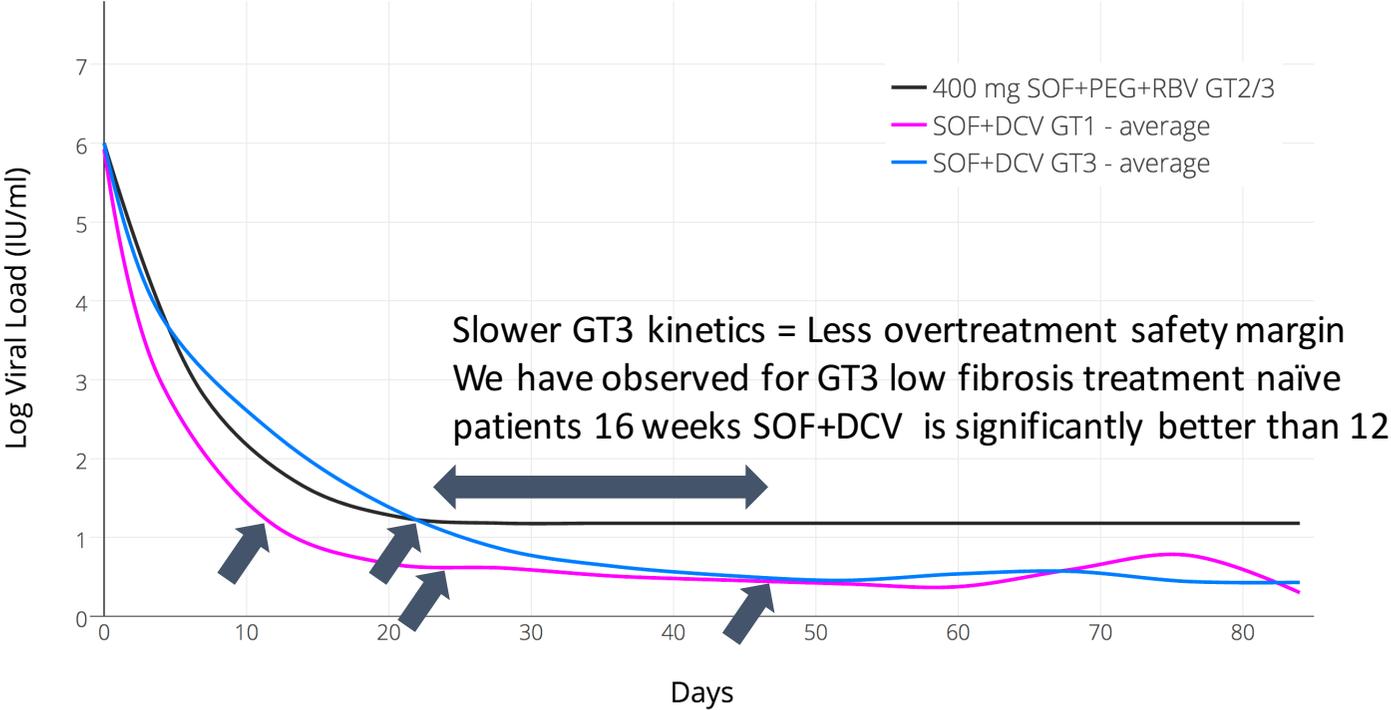
SVR12 has proven durable through to SVR24 and SVR52 in all the patients for whom these results are currently available (over 60%)

Empirical Relapse Analysis

- Three on treatment virological failures. 1 x S282T, 2 x Y93H
 - 2 failed around week 7, one undetected at 8 weeks but 120 at EOT
 - NS5A monotherapy fails around week 6-8
 - Sofosbuvir is an inactive pro-drug that requires CatA and CES1 ?deficiency
- 10 cirrhotics prescribed 12 weeks courses – only 2 with RBV
 - Insufficient duration and intensity of treatment, for which I can take the blame
 - Most were treatment experienced and reluctant to revisit RBV
- 12 week Harvoni[®] failure unsurprisingly failed 12 weeks SOF+DCV
 - Follow Jordan Feld's advice to pick at least two of longer, stronger, and add RBV

Is 12 SOF+DCV weeks enough for GT3?

On Treatment Viral Load SOF+DCV GT1 vs GT3

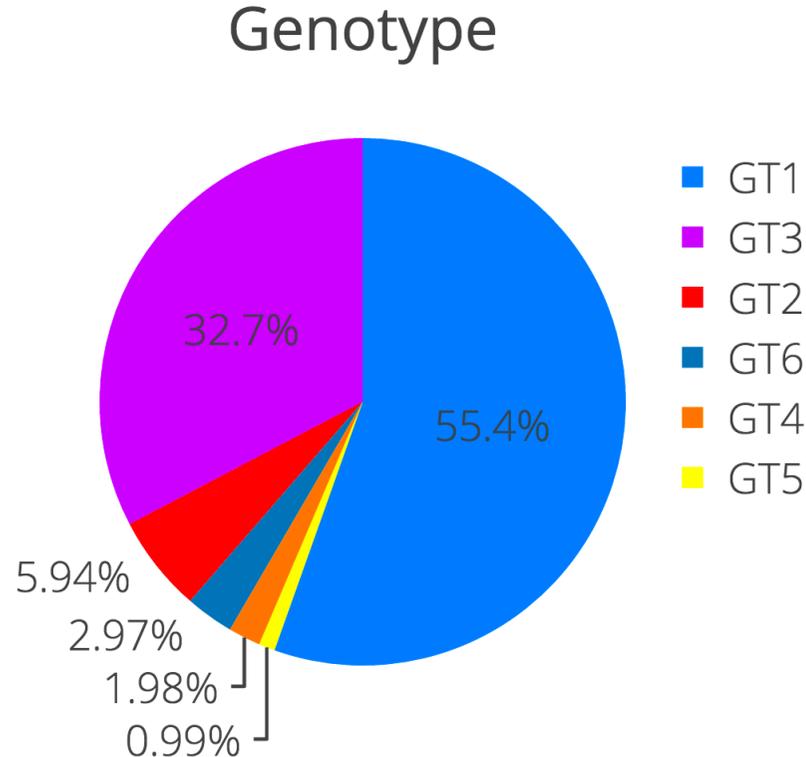


Generics DAAs Around the World

- 1160 generics patients have data being collated in London
 - Sourced generic SOF, LDV, DCV, VEL and RBV
 - Suppliers in India, Bangladesh, China and Egypt
- 4 cohorts
 - Including the one just described
- 240 locations in 88 countries spanning 5 continents
 - Hospitals, clinics and private doctors
- All having routine monitoring
 - Patient HCV RNA levels were evaluated pre-treatment, during treatment, at end of treatment (EOT) and then for SVR4, SVR12, and SVR24

Baseline Characteristics

n	1160
SOF	2.1% (24/1160)
SOF+RBV	5.7% (66/1160)
SOF+LDV	39.0% (452/1160)
SOF+LDV+RBV	4.8% (56/1160)
SOF+DCV	40.9% (475/1160)
SOF+DCV+RBV	7.5% (87/1160)
Cirrhosis	18%
Male	61%
Mean Age	49 years
Mean HCV RNA	6.6 log IU/ml 4002711 IU/ml



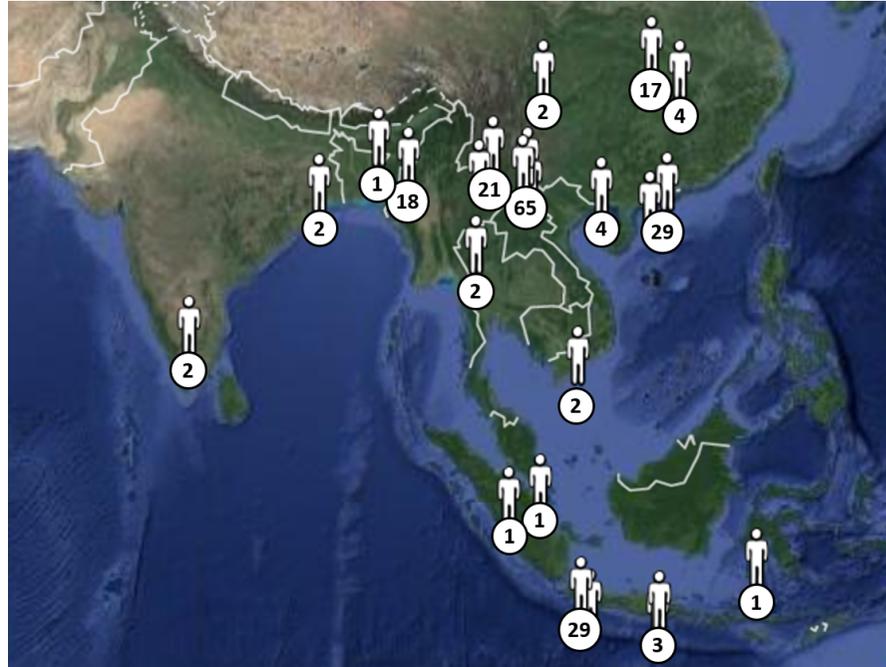
Results: Cohort 2

- n=226
- GT1,2,3,4,5
- SVR4: 98%
(122/125)
- SVR12: 97%
(94/96)

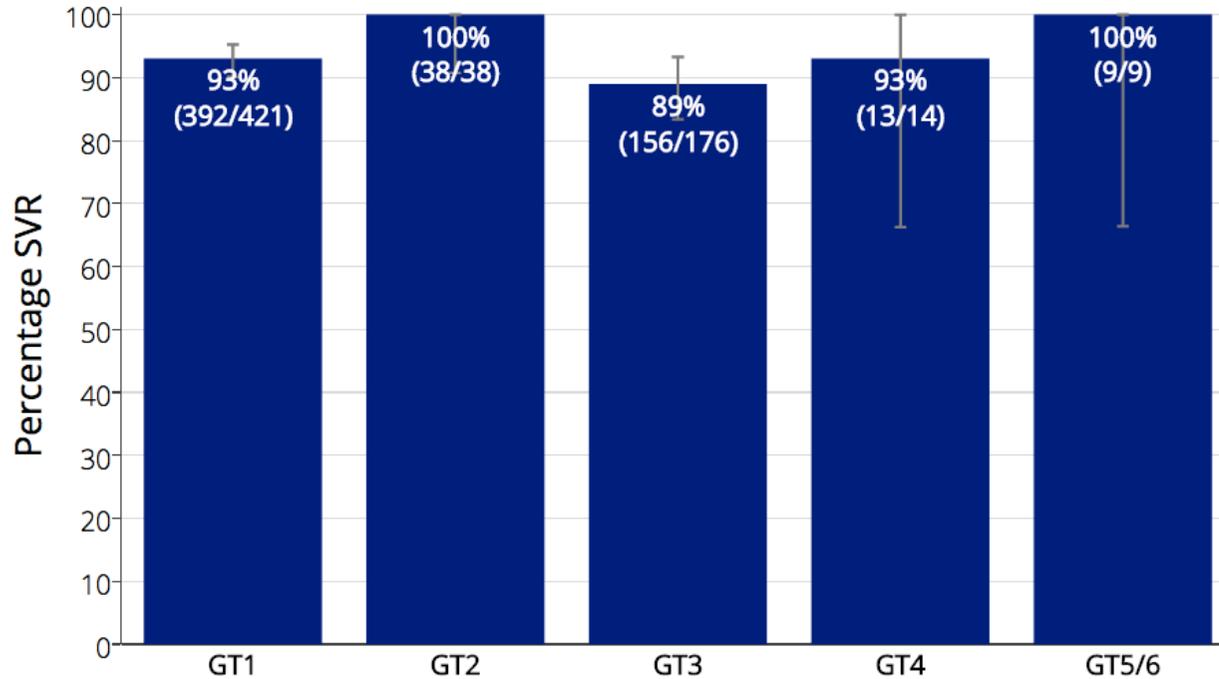


Results: Cohort 3

- n=263
- GT1,2,3,4,6
- SVR4: 100%
(79/79)
- SVR12: 93%
(53/57)



Global SVR12 Results for HCV Generics



1. Genotype 2 results almost entirely SOF+DCV supporting the recent EASL changes to guidelines (Australia, can we please make this change? SOF+RBV is outdated)
2. Aggregated results for cohorts 1-4. Cohort 1 final. Cohorts 2-4 interim.

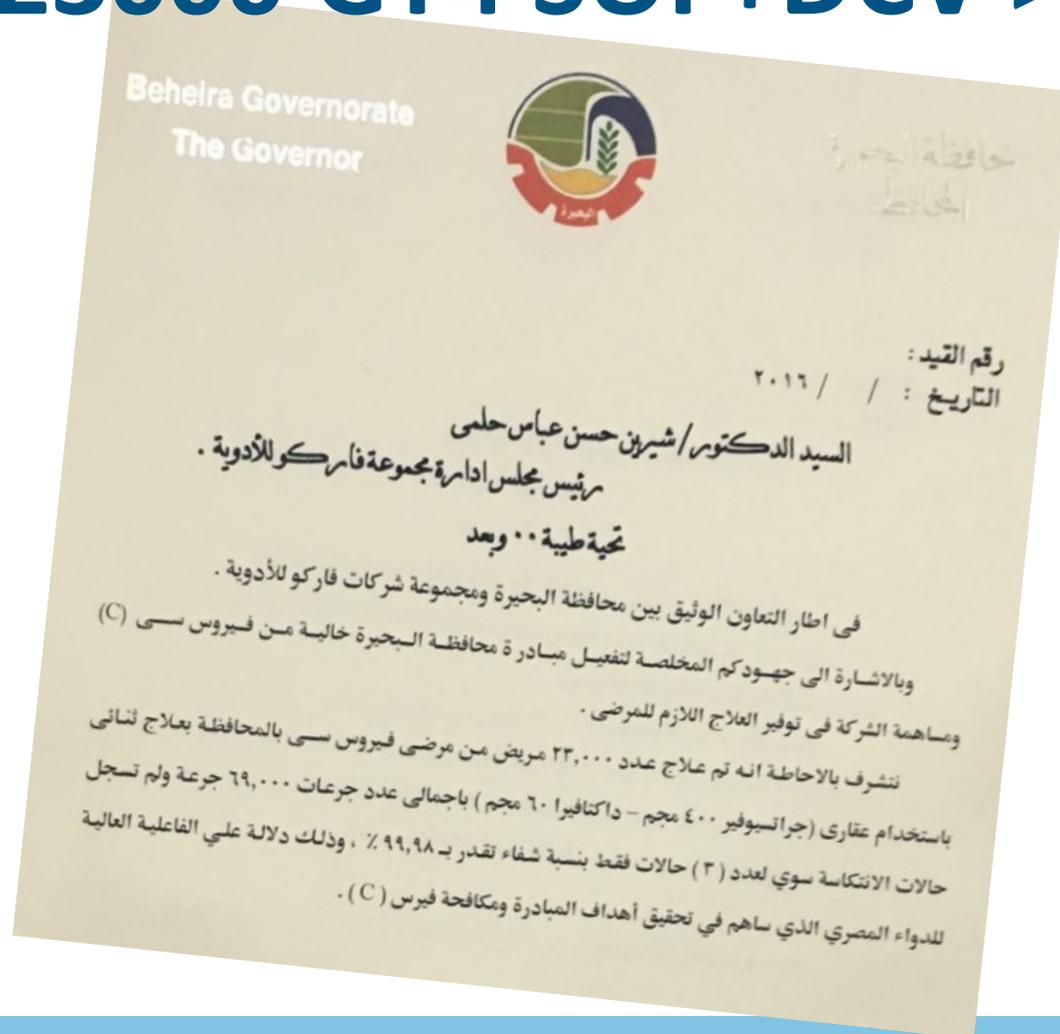
2016 Was A Big Year For HCV Generics

- Production of high quality generic DAAs commenced at scale
 - Factories in Algeria, Bangladesh, Egypt, India, Morocco and Pakistan
 - Most CGMP, FDA, EMA, WHO Prequalified for HIV and other generics
- There was a lot of protesting about prices and patent validity while quietly, in the background.....
- **Generic DAAs overtook branded medications as the dominant source of worldwide cure**
- In Egypt alone >1 million patients have been treated with DAAs¹
 - They have the ambitious target of cure for all by 2020² (realistically 2030)

1. <http://www.egfrhep.com/2016/The%20Egyptian%20National%20HCV%20Control%20Program.pdf>

2. <http://www.egyptindependent.com/news/egypt-be-free-hepatitis-c-2020-health-minister>

Egypt n=23000 GT4 SOF+DCV >95% SVR



Bioequivalence has been demonstrated



Randomized, four-way, four-period, fully replicated, single oral dose, open-label, crossover, bioequivalence study to compare Sofosbuvir tablets (400 mg sofosbuvir) produced by European Egyptian Pharmaceutical Industries, versus Sovaldi® tablets (400 mg sofosbuvir) produced by Gilead Sciences, in healthy subjects under fed conditions

Document Code: SFR-472-431, V.01

BIOEQUIVALENCE STUDY FINAL REPORT

Sponsor	European Egyptian Pharmaceutical Industries (EEPI) KM25, Alex/Cairo Desert Road, Amriya, Alexandria, Egypt. Tel/Fax: +2 03 4700199
Sponsor's Representative	Sherine Helmy - CEO Contact Person: Hanaa Abdel-Maguid Title: R&D Innovation Projects Head E-mail: hanaa@pharco.org Mobile: +201008986775
Contract Research Organization	ACDIMA BioCenter for Bioequivalence and Pharmaceutical Studies- P. O. Box: 925161 Amman 11190, Jordan Tel: + 962 – 6 – 582 1618 Fax: + 962 – 6 – 585 3719 E-mail: biocenter@acdima.com
CRO Representative	Mohammad Khalil Mohammad, R.Ph., Ph.D., Executive Director/CEO ACDIMA BioCenter E-mail: mkmohammad@acdima.com

In The 51% Red Zone, Bioequivalent Generics Do Not Arrive Until 2032...



Data: Gilead Treatment Expansion News, Winter 2016/2017, Jan 2017. Gilead License Factsheet, July 2016. Gilead Sovaldi registration, July 2016. Center for Disease Analysis, Polaris Observatory, April 2017. Blach et al, Lancet Gastroenterol Hepatol; 2(3):161–76. Gower et al. 2014, Journal of Hepatology 2014 vol. 61 j S45–S57.

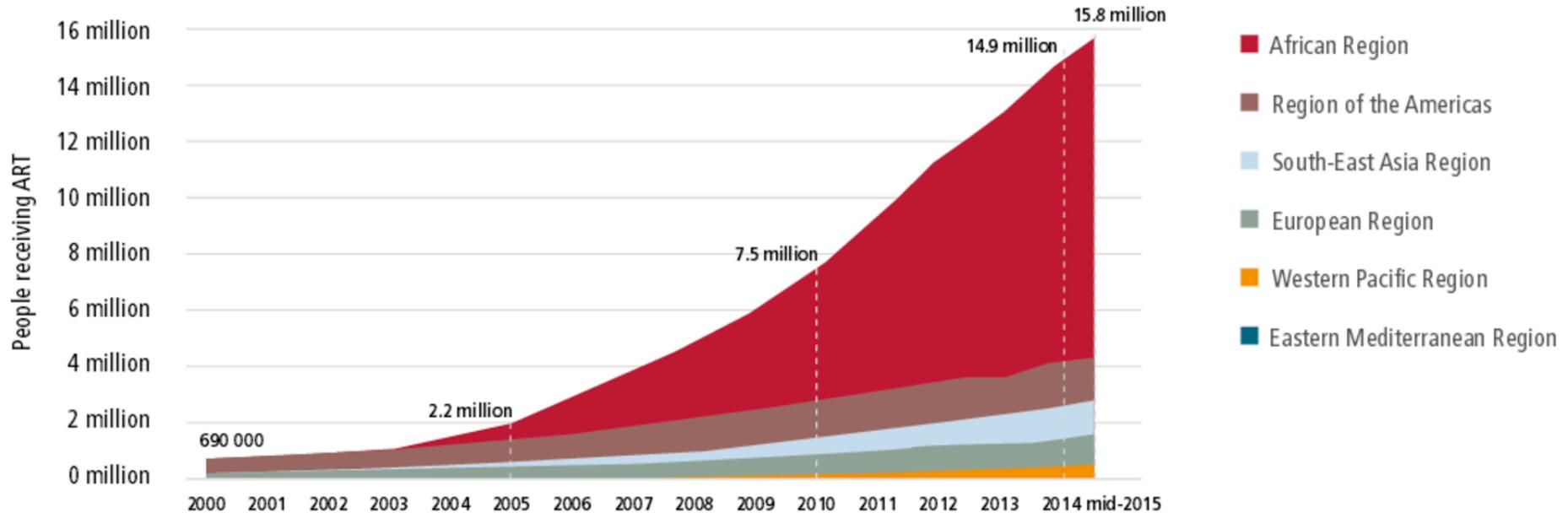
We've Been Here Before – With HIV

- In 2001 Yusef Hamied announced that Cipla would produce generic HIV medication for a treatment cost of \$1/day¹
- In 2004 the Lancet published a study demonstrating that this generic HIV medication worked as expected²
- Bioequivalence studies and WHO prequalification followed
- At the same time the South African government got serious
 - Parallel imports of generic HIV medication forced the drug companies back to the negotiating table, with the direct result that.....
 - The \$10,000/patient/year cost fell to more affordable levels

1. <http://amfar.org/Articles/Around-The-World/TreatAsia/Older/An-Interview-with-Cipla-s-Yusef-Hamied%E2%80%94Indian-Drug-Maker-Leads-the-Charge-for-Low-Cost-AIDS-Drugs/>
2. [http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(04\)16586-0/fulltext](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(04)16586-0/fulltext)

This Graph Shows the Global Impact...

Estimated numbers of people receiving antiretroviral therapy globally and by WHO Region and percentage coverage globally, 2000–2015



Conclusions

- Treatment with generics works
 - Generics worked for HIV to apply market forces to prices
- Margaret Mead once said
 - “Never doubt that a small group of thoughtful, committed citizens can change the world; indeed, it's the only thing that ever has”
- Unless we doctors start being more proactive you can foresee a time where, on current trends, medications are priced out of reach for all but the super rich
- The WHO has the goal to eliminate Hepatitis C by 2030
 - Our patients are depending on our leadership to see this goal realized
- Developing a cure for Hep C was a breathtaking achievement
- Let’s work together, do what we can, use the tools for their intended purpose, and make the eradication of Hep C our next great achievement.



Hep C Cure Club

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Two Bulls
m2bulls.com



SORRY,
I CAN'T
LET YOU IN!
YOU'RE
NOT SICK
ENOUGH.



More Information

- [http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(16\)32051-7/fulltext](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(16)32051-7/fulltext)
- <http://onlinelibrary.wiley.com/doi/10.1111/liv.13157/full>
- <http://www.who.int/hepatitis/publications/hep-elimination-by-2030-brief/en/>