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 suggsted 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
$84,00XX
Generic Hep C Cure
$1,50X
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Background

- Unaffordable prices prevent patient access
- Generic DAAs are being mass produced at low cost
  - 1% of the current US retail price[1], 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 Australia[2], the UK[3], and many other countries, individuals have the right to import a three month supply of medication, for their personal use.

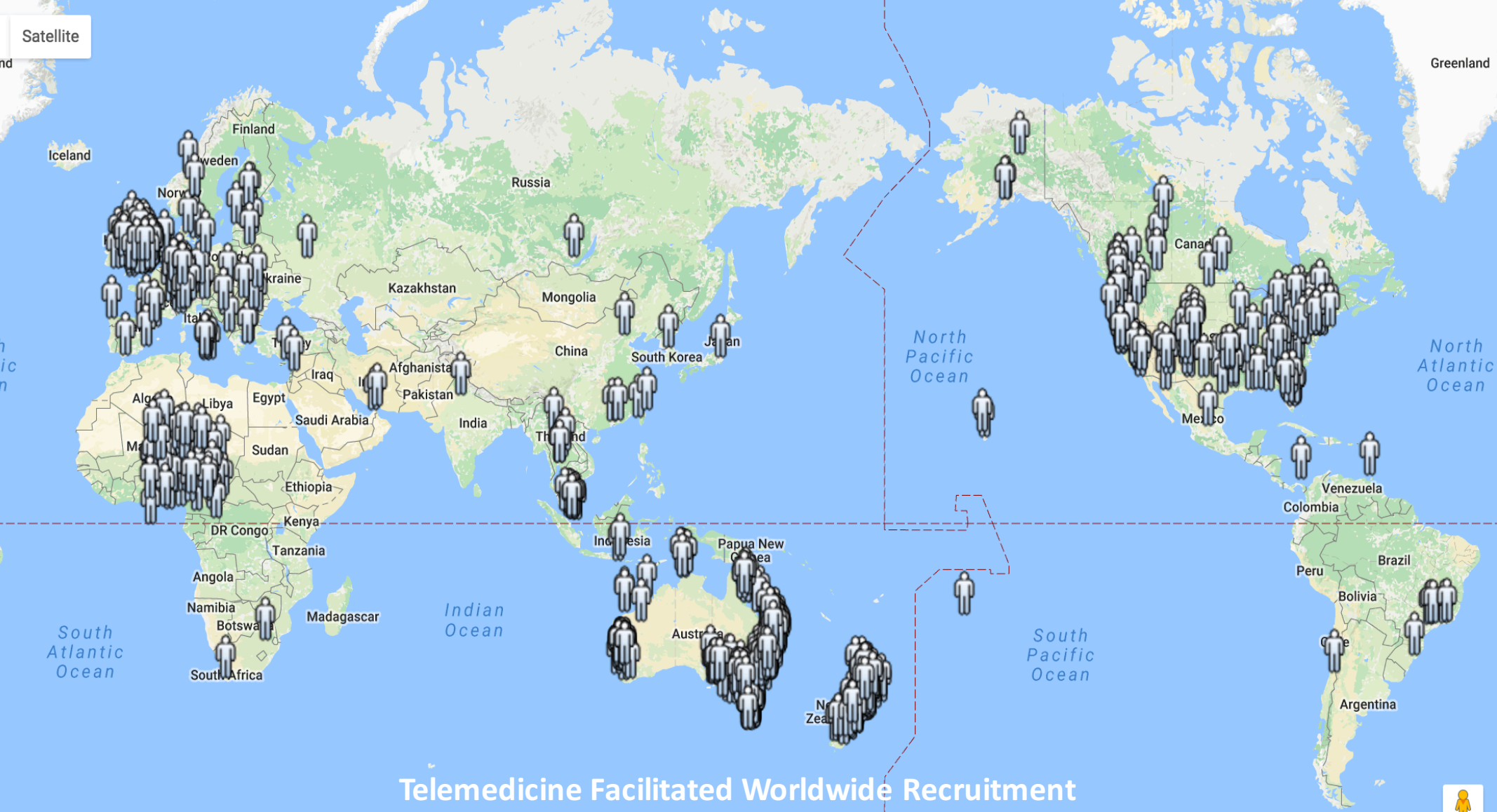
1. Hill A. Minimum Costs for Producing Hepatitis C Direct-Acting Antivirals. Clin Inf Dis. 2014
2. https://www.tga.gov.au/personal-importation-scheme
3. https://www.gov.uk/government/organisations/hm-revenue-customs

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

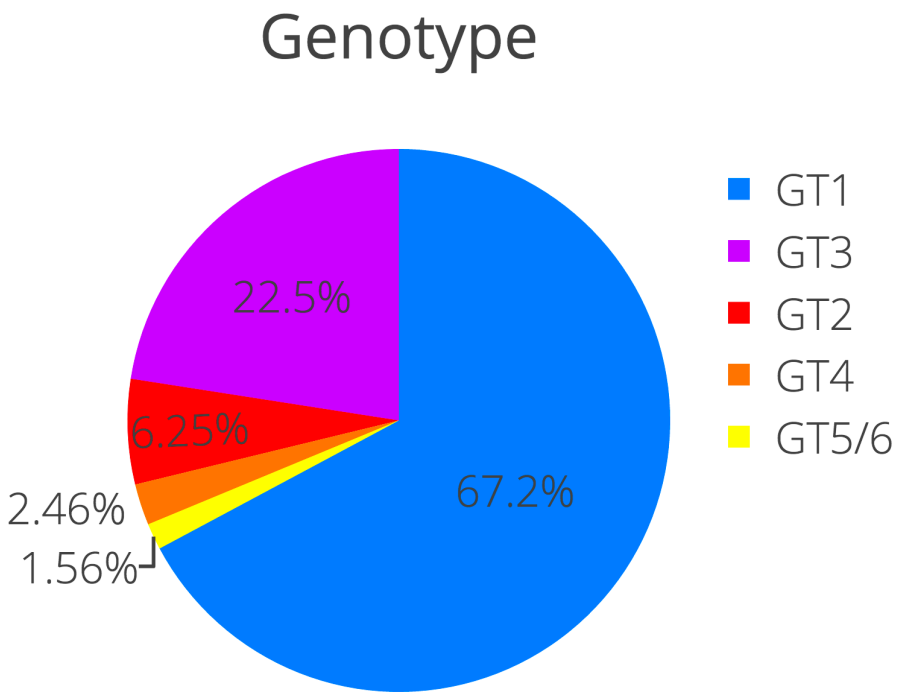
- Generic DAAs were evaluated for quality
  - Tested with HPLC, NMR and Mass Spectrometry
- 448 consecutive patients enrolled
- Underwent routine assessment
  - Baseline, on treatment, and post treatment for SVR4, SVR12 and SVR24
- Objective was to answer two key clinical questions:
  - Do generics work?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



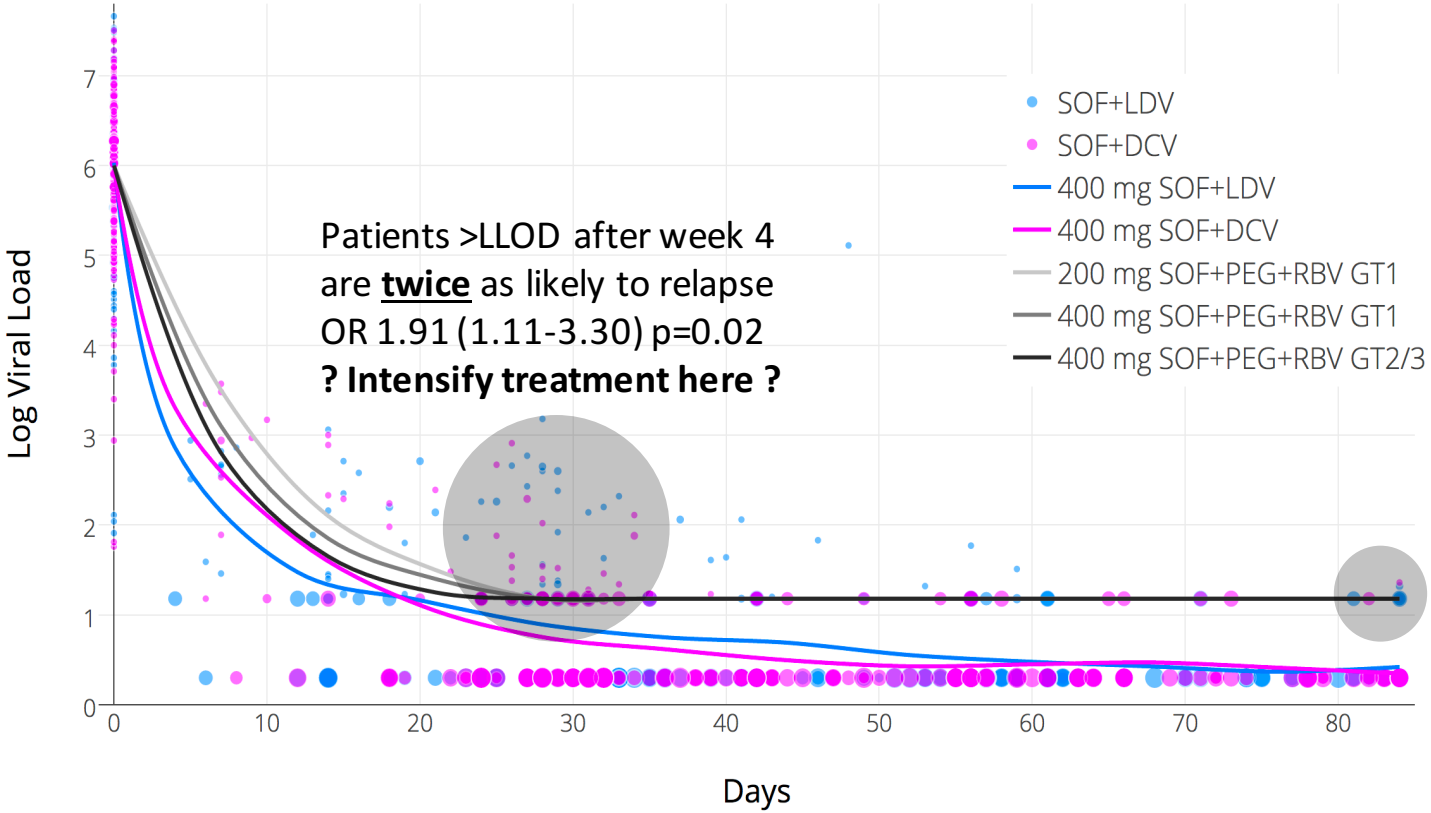
Telemedicine Facilitated Worldwide Recruitment

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



75% (24/32) went on to achieve SVR12 after being <LLOQ but >LLOD at EOT

SOF+PEG+RBV kinetics data source:
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 Patients**[1]

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

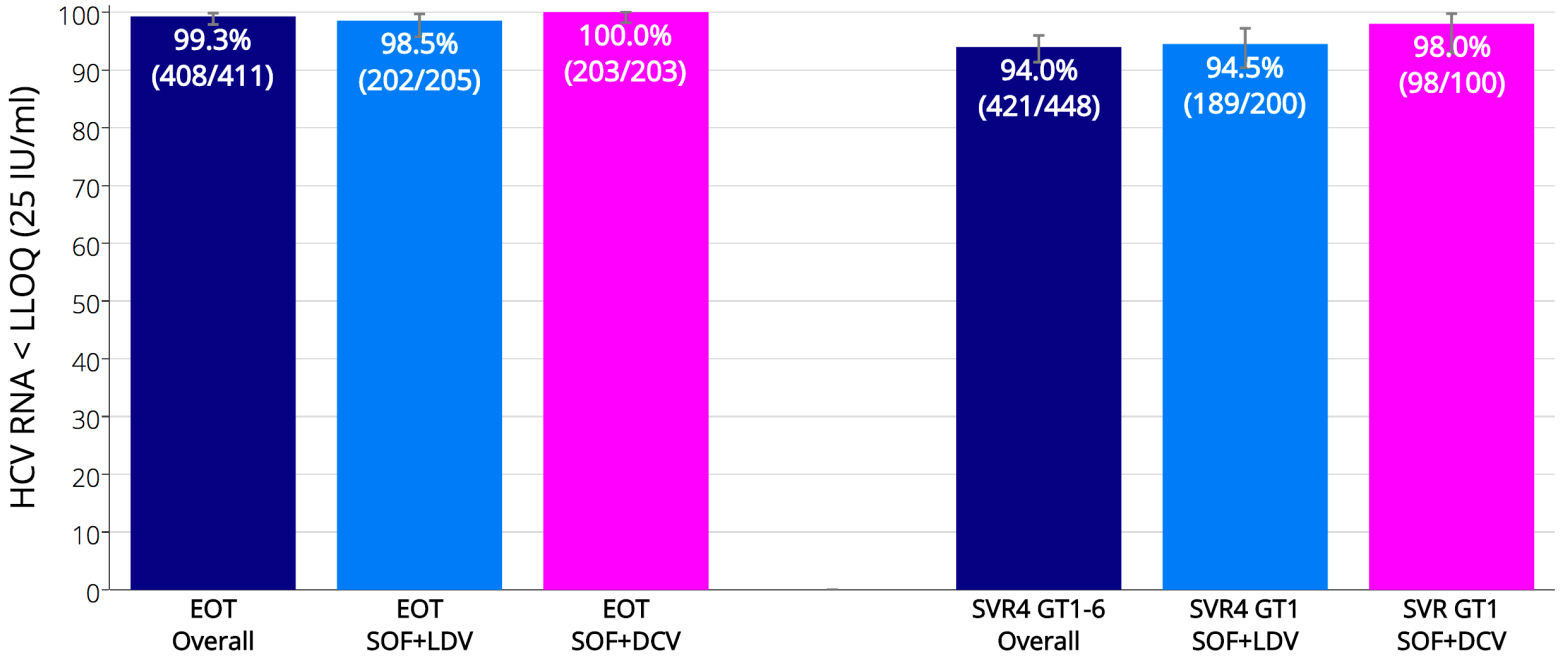
1. If we can cheaply and easily identify a group of patients at much higher risk of failure, at a time when we can do something about it, then we can intensify treatment
   - C-SWIFT Zepatier + Sofosbuvir[1] – Salvage rate 100% (23/23) with 80% baseline RAVs
   - QUARTZ-1 Viekira + Sofosbuvir[1] – Salvage 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/301490/

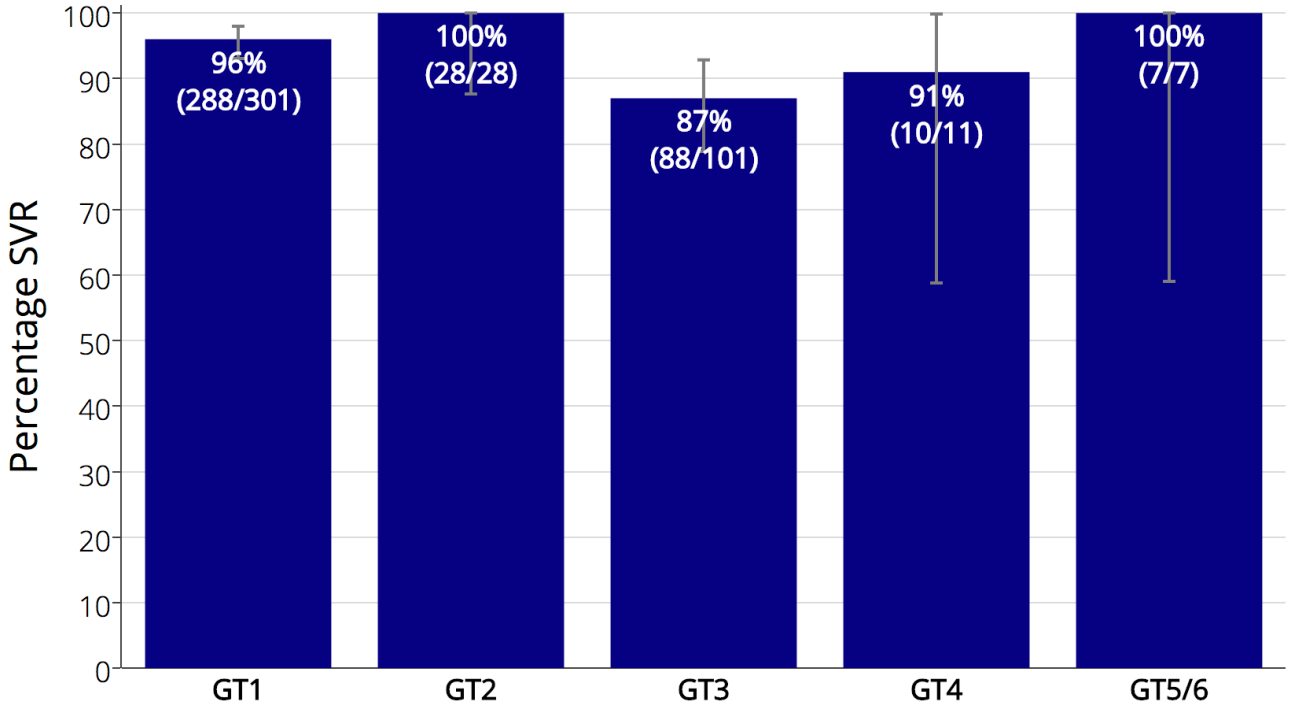
Patient Safety

- 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

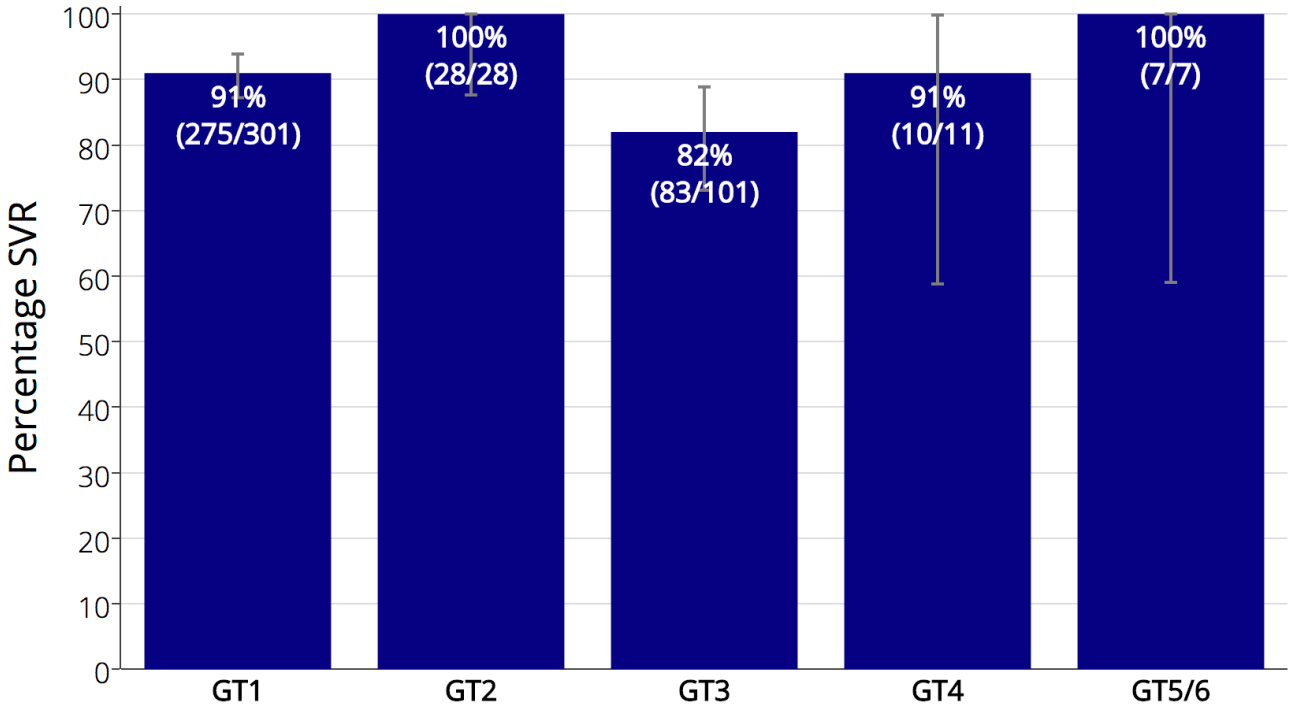
HCV RNA < LLOQ at EOT and SVR4



SVR4 Results by Genotype



SVR12 Results by Genotype



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

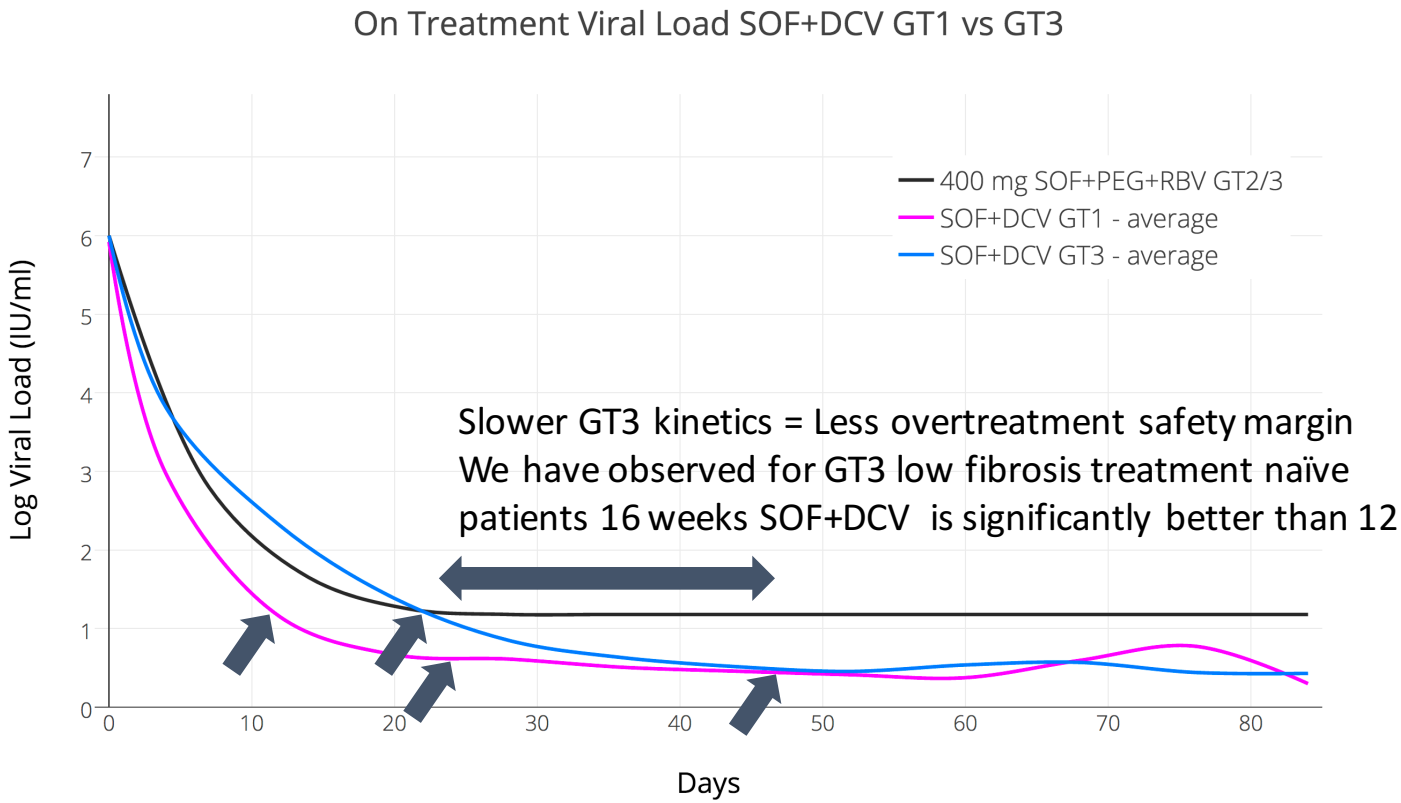
HCV RNA <25 IU/ml		
RVR:	85.7% (198/231)	CI 80.5% - 90.0%
EOT:	99.3% (408/411)	CI 97.9% - 99.8%
SVR4:	94.0% (421/448)	CI 91.3% - 96.0%
SVR12:	90.0% (403/448)	CI 86.8% - 92.6%
LTFUP:	0.4% (2/448)	

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 monotherpay 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?

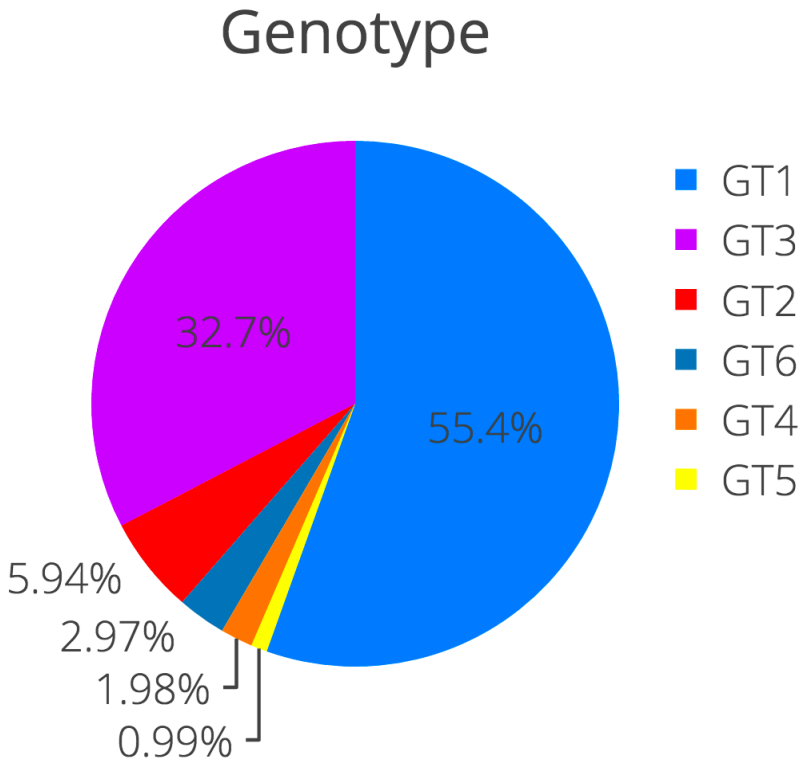


Generics DAAs Around the World

- 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

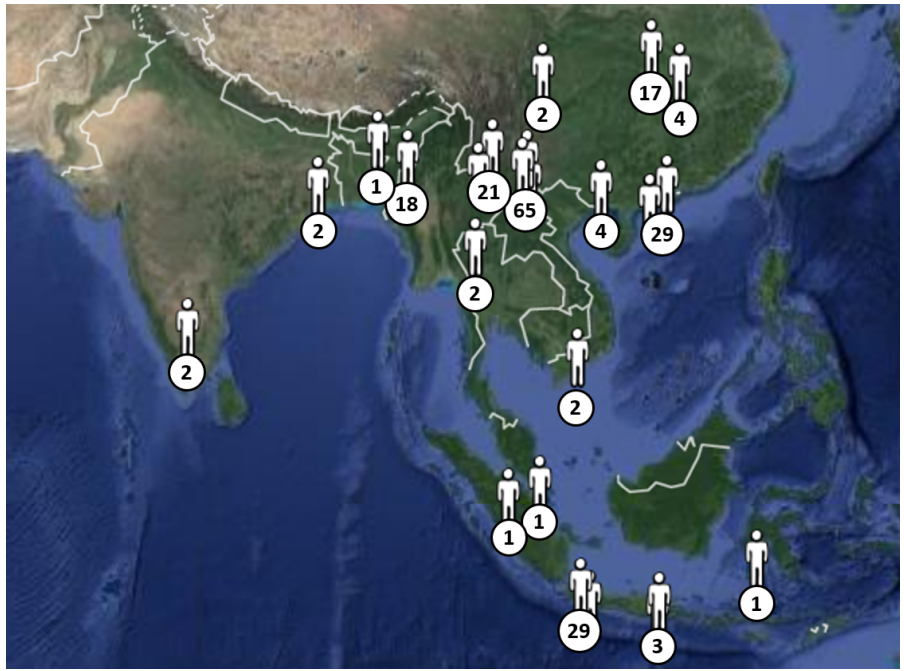


Results: Cohort 2

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

Results: Cohort 3

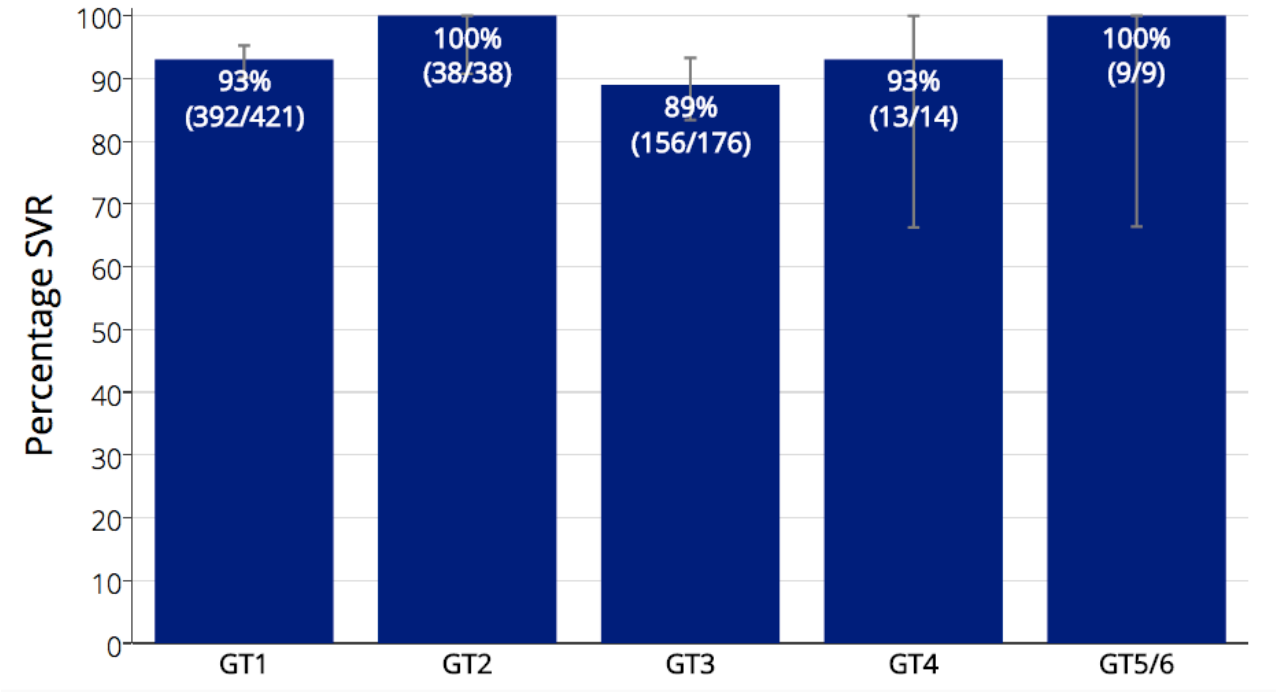
- n=263
- GT1,2,3,4,6
- SVR4: 100% (79/79)
- SVR12: 93% (53/57)



Results: Cohort 4

- n=224
- GT1b,2,3
- SVR4: 100% (105/105)
- SVR12: 98% (75/76)

Global SVR12 Results for HCV Generics



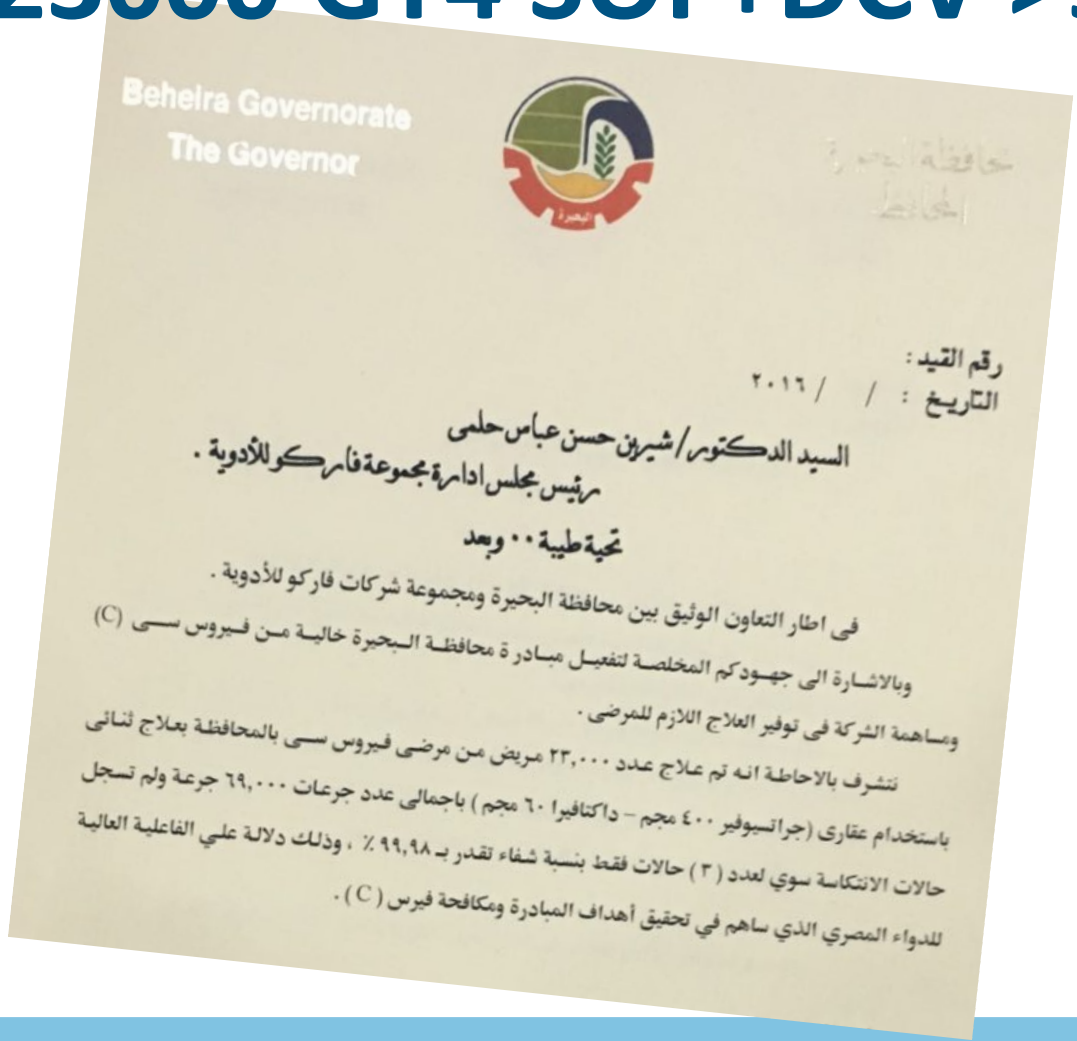
1. Genotype 2 results almost entirely SOF+DCV supporting the recent EASL changes to guidelines (Australia, can we please make this change? SOF+RBV is outdated)
2. Aggregated results for cohorts 1-4. Cohort 1 final. Cohorts 2-4 interim.

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 DAAs[1]
  - They have the ambitious target of cure for all by 2020[2] (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



Beheira Governorate
The Governor

رقم القيد :
التاريخ : / / ٢٠١٦

السيد الدكتور/ شيرين حسن عباس حلمى
رئيس مجلس ادارة مجموعة فاركو للأدوية .

تحية طيبة .. وبعد

فى اطار التعاون الوثيق بين محافظة البحيرة ومجموعة شركات فاركو للأدوية .

وبالاشارة الى جهودكم المخلصة لتفعيل مبادرة محافظة البحيرة خالية من فيروس سى (C)

ومساهمة الشركة فى توفير العلاج اللازم للمرضى .

نتشرف بالاحاطة انه تم علاج عدد ٢٣,٠٠٠ مريض من مرضى فيروس سى بالمحافظة بعلاج ثنائى

باستخدام عقارى (جرانسيوفير ٤٠٠ مجم – داكتافيرا ٦٠ مجم) باجمالى عدد جرعات ٦٩,٠٠٠ جرعة ولم تسجل

حالات الانتكاسة سوي لعدد (٣) حالات فقط بنسبة شفاء تقدر بـ ٩٩,٩٨ ٪ ، وذلك دلالة علي الفاعلية العالية

للدواء المصري الذي ساهم في تحقيق أهداف المبادرة ومكافحة فيرس (C) .

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

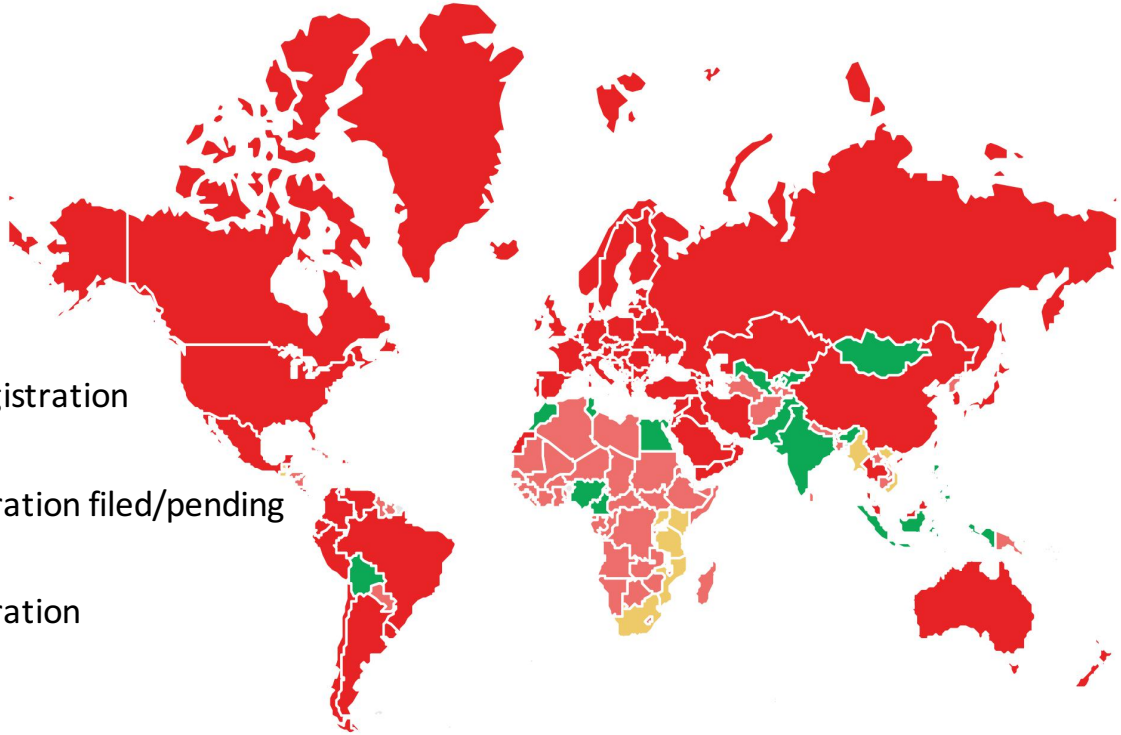
Document Code: SFR-472-431, V.01

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…

- No voluntary license (51% global epidemic)
- Voluntary license, no SOF registration (6% global epidemic)
- Voluntary license, SOF registration filed/pending (1% global epidemic)
- Voluntary license, SOF registration (42% global epidemic)



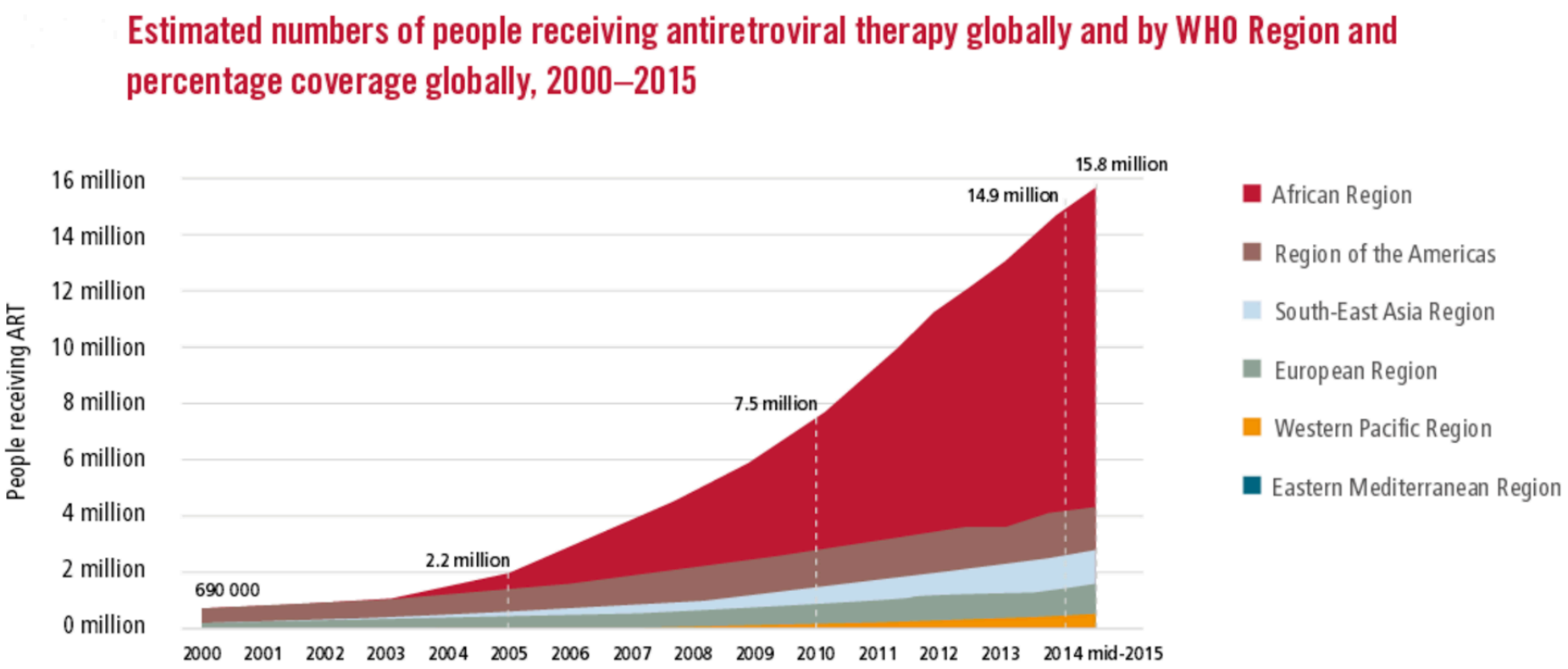
Data: Gilead Treatment Expansion News, Winter 2016/2017, Jan 2017. Gilead License Factsheet, July 2016. Gilead Sovaldi registration, July 2016. Center for Disease Analysis, Polaris Observatory, April 2017. Blach et al, Lancet Gastroenterol Hepatol; 2(3):161–76. Gower et al. 2014, Journal of Hepatology 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/day[1]
- In 2004 the Lancet published a study demonstrating that this generic HIV medication worked as expected[2]
- 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-Yusuf-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

This Graph Shows the Global Impact…



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.


NOhep


Hep C Cure Club
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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://onlinelibrary.wiley.com/doi/10.1111/liv.13157/full
- http://www.who.int/hepatitis/publications/hep-elimination-by-2030-brief/en/