Implementation of Pediatric HCV Treatment in LMIC

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PIM 2017
27th - 30th April 2017, San Servolo, Venice

Disclosure speaker interests

Disclosure of speaker interest

Travel to international meetings in the last two years has been supported by pharma (Abbvie, Gilead and Quadri-Pharma)

Member of Advisory board of Perspectum-Liver Multiscan

Investigator Initiated Trial supported by Gilead Sciences for use of Harvoni in childre and adolescents undergoing chemotherapy

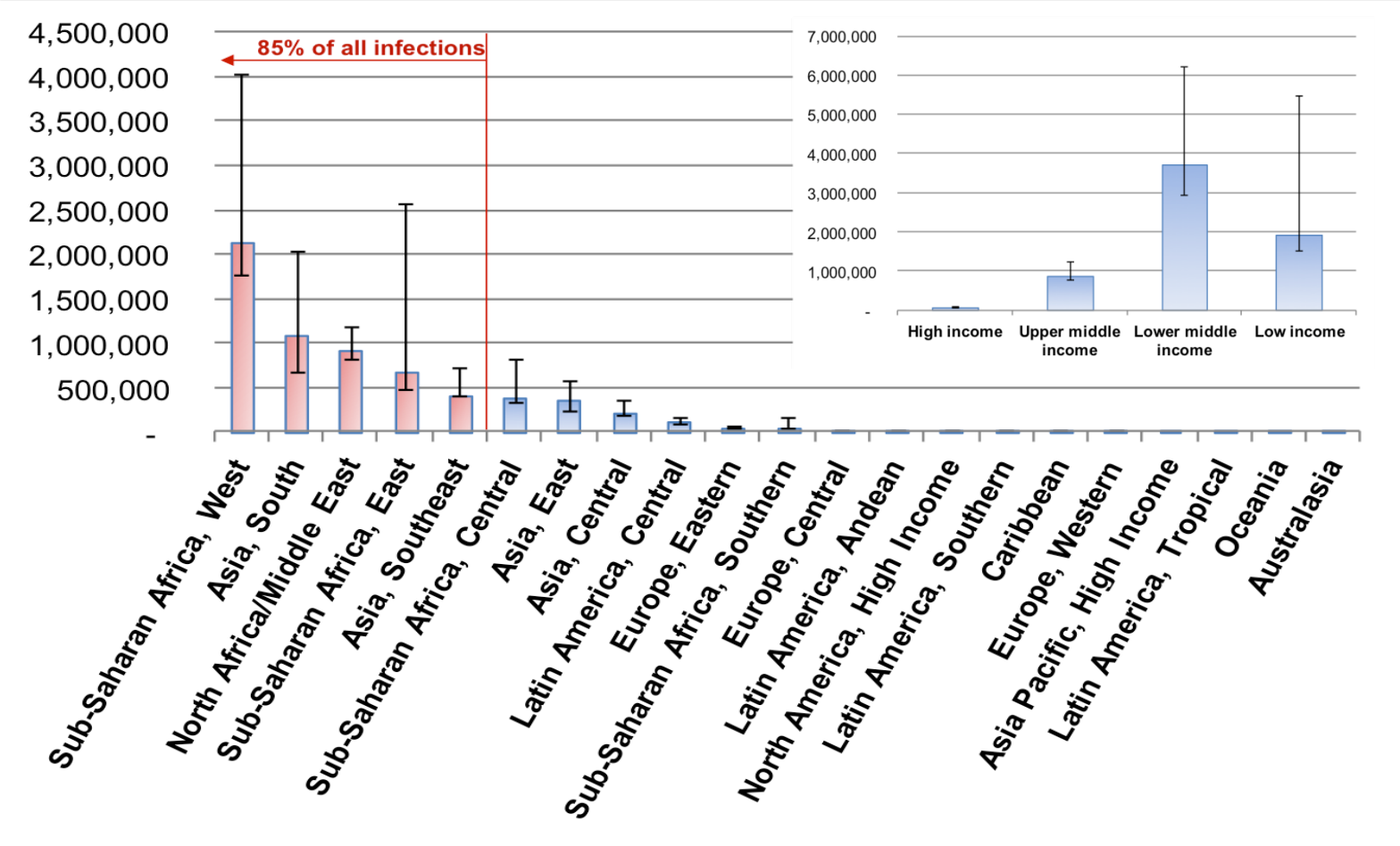
Why HCV in Children?

Diagnosis

- Infection is mostly asymptomatic
- Children do not undergo biochemical testing or donate blood
- Many children with HCV have normal ALT values
- Risk factors are not known or sought by care-providers
- Extrahepatic manifestations are rare
- Pediatricians do not consider HCV infection

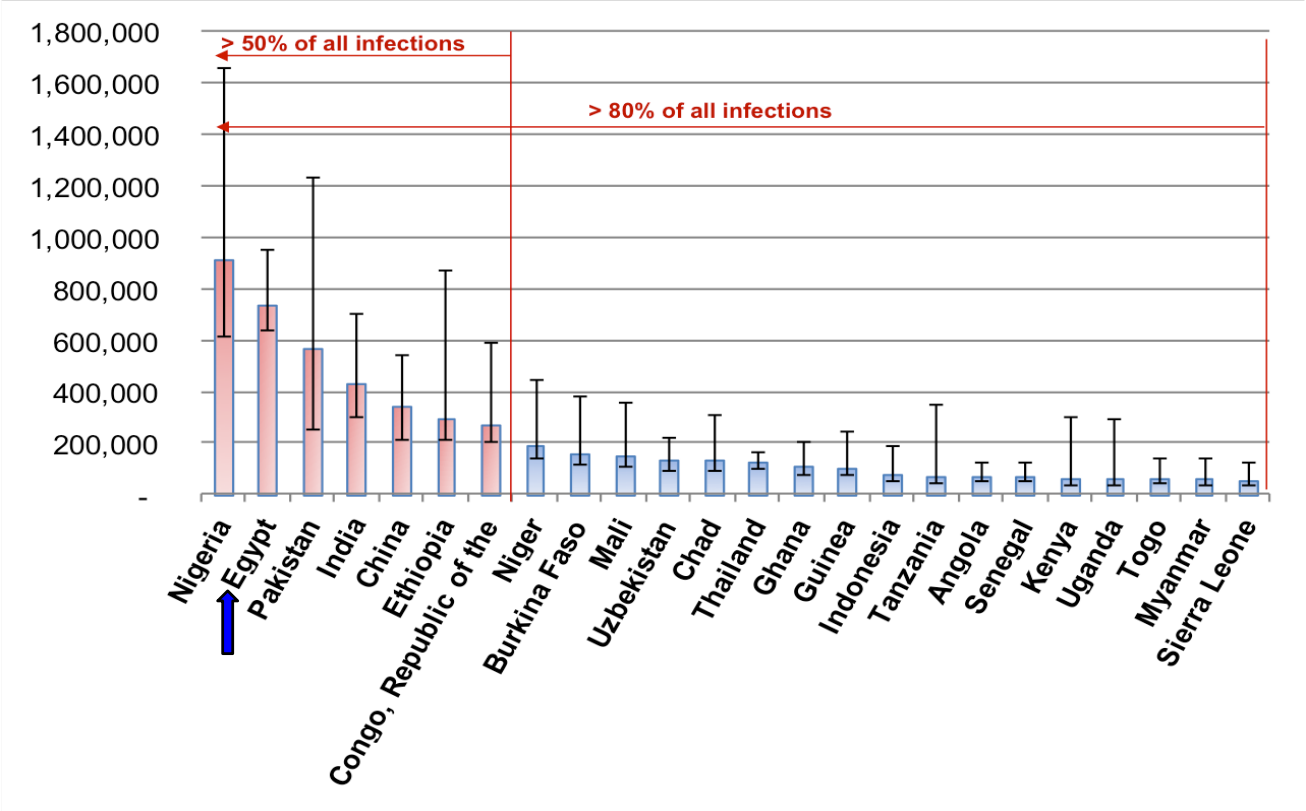
BURDEN LARGELY UNKNOWN

Global Burden of HCV in Children <15 years



El-Sayed and Razavi, Global Estimate of HCV Infection in The Pediatric and Adolescent Population , (2015). P1263. J Hepatol;62:S831–S832.

Global Burden of HCV in Children <15 years



-Viremic prevalence was lowest in *"high income countries"* at 0.3% (0.03-0.5%) and highest in "*low income countries*" at 0.6% (0.1-1.0%).

-There are 6.6 (6.1-11.6) million viremic infections.

El-Sayed and Razavi, Global Estimate of HCVInfection in The Pediatric and Adolescent Population , (2015). P1263. J Hepatol;62:S831–S832.

Prevention of MTCT of HCV

- HCV:

- In the absence of a vaccine for HCV, we need to improve HCV *risk screening*, including children born to HCV-infected mothers
- No therapeutic agents are yet available or recommended to decrease the risk of MTCT of HCV, which remains 3 to 10%.
- HCV MTCT can be minimized by avoiding **fetal scalp electrodes* and **birth trauma* whenever possible.
- Young women with HCV should be referred for treatment post delivery, and neonates should be closely followed to rule out infection.

Pregnancy Outcomes with HBV and HCV

- Pregnancy in patients with chronic HBV or HCV is associated with MTCT and may be associated with increased maternal and fetal complications.

- HCV vertical transmission occurs in 5.8% (95% confidence interval= 4.2%–7.8%) of infants born to women who are infected only with HCV and in up to twice as many infants born to women who are also infected with "*HIV*" or who have "*high HCV viral Loads*".

HBV and HCV
Preterm birth
Low birth weight
Premature rupture of membranes
Gestational diabetes
Possible small increase in congenital anomalies
HCV
Cholestasis of pregnancy
NICU admission
Neonatal abstinence syndrome

Pregnancy outcomes with HBV and HCV

Dunkelberg et al, J Perinatol; 34(12):882-91, 2016.
Benova et al, Clin Infect Dis;59:765-73, 2014.
Kanninen et al, Hepatology; 62:1656-8, 2015

Dunkelberg et al, J Perinatol; 34(12):882-91, 2016

Egyptian Children at Risk of HCV Infection

- Recurrent blood or blood product transfusion or multiple invasive procedures
- Children born to HCV-infected mothers
- Children with an infected house-hold member
- Adolescents with high risk behavior (illicit drug use)

Transmission Essentially Related to Medical Care

- *Medical injections*: intravenous and IV infusions.
- *Stitches* and *surgery*.
- *Dental care*: periodontal treatment.
- Obstetrics.
- *Intrafamilal transmission*: limited to ≈10% of incident cases.
- Not much is known about IDU, 1-3% of study controls (low socio-economical status)

The R0 of the spread of HCV without treatment was 3.45

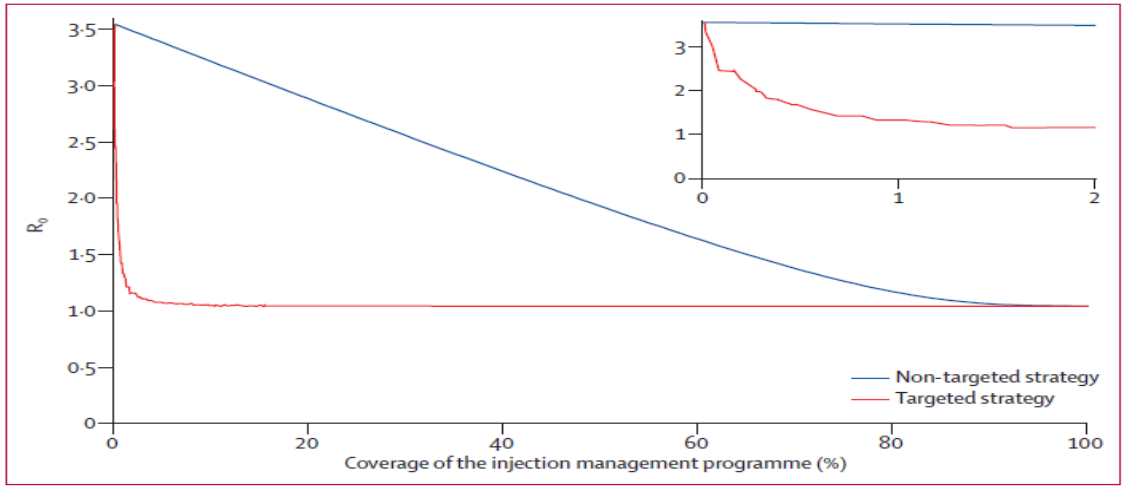


Figure 3: **The potential effect of injection control on the severity of the spread of hepatitis C virus**
The graph shows R_0 (mean of bootstrap distributions) decline versus the coverage of the injection management programme after a non-targeted and targeted strategy. The black graph shows the result of including an increasing number of individuals under injection management, regardless of their health-care practices. The red graph shows the epidemiological effect of injection management when enrolled individuals are prioritised by their injection rates. The inset displays a zoom-in of the main panel in the region of low coverage.

Berban et al, 2014

HCV Prevalence Studies in Egyptian Children

- *Perinatal HCV* in ***1,863 mother-infant pairs*** in rural Egyptian villages.
- 15.7% and 10.9% of pregnant women were anti-HCV and HCV-RNA +ve respectively.
- Among 329 infants born of these mothers, *33 (10.0%)* WERE +ve for both anti-HCV and HCV-RNA *2 months* following birth.

Shebl et al, J Med Virol, 2009

- Incidence of *community-acquired infection in children* in 3 Egyptian villages.
- 2852 uninfected infants were prospectively followed, the incidence was 3.8/1000 PY during infancy and for the 1-5-years age group.

Saleh et al, Trans R Soc Trop Med Hyg. 2010

HCV Prevalence Studies in Egyptian Children

- 1042 children 1-9 years were screened, asymptomatic HCV infection was detectable in 2.02% Egyptian children. *(El-Raziky et al, WJG 2007)*

- HCV intrafamilial clustering was reported more from sibling-sibling (31%) and to a lesser extent from mother-child (23%), Father-child (12%) or husband-wife (6%) *(Plancoulaine et al, 2008)*

- 500 children, age between 6 and 15 years, were selected from 10 schools in Alexandria, Egypt. HCV seroprevalence was 5.8%, with HCV viraemia in 75% of the studied children

(Barakat and El-Bashir, J Viral Hepat, 2011)

Prevalence in Children <15 years National Surveys

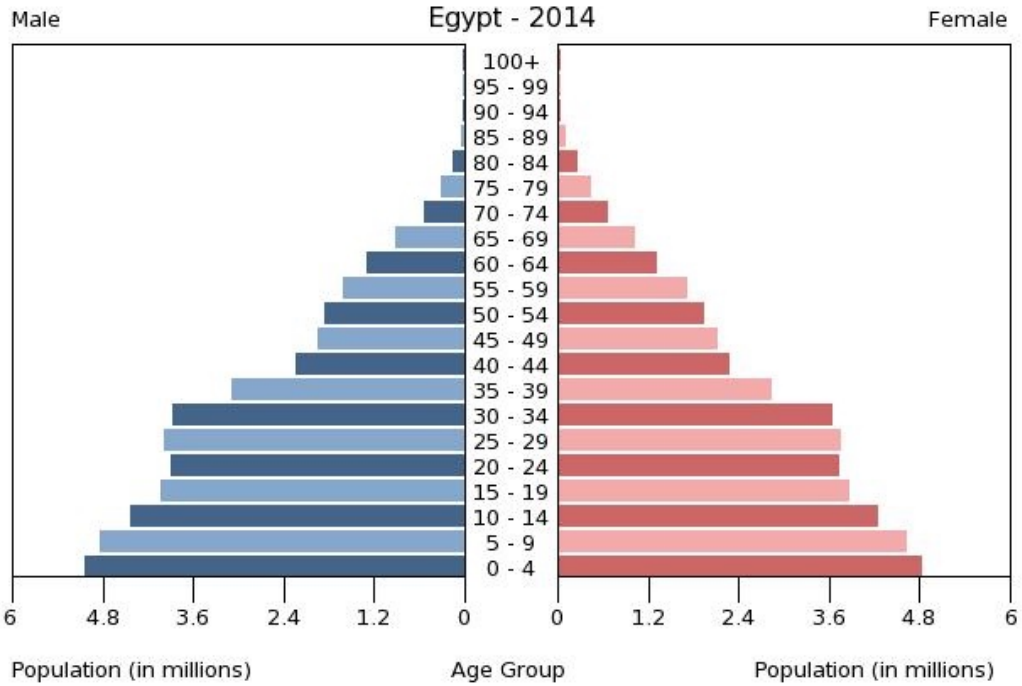
- *MOH Survey 2009*: prevalence of HCV for *3678* Egyptian children from 1-15 years old in 8 representative Governorates.
- The prevalence for HCV was 0.5%
- HCV infection was higher among rural than urban residents (0.5%

  compared with 0.2%). Males are also more affected (0.5%) than

  females (0.3%).

- *DHS survey 2015:* prevalence of 0.2-0.5% between ages 0 and 15 yrs

Egyptian Population Demographics



- More than 100,000 < 15 years may be chronically infected with HCV

- >10,000 are born yearly with HCV (*DHS survey 2015*: 7% HCV viremia among the Egyptian population (15-59 years)

0-14 years: 32.1% (male 14,272,494/female 13,639,550)
15-24 years: 17.8% (male 7,913,351/female 7,536,925)
Rate of births: 23.35 births/1,000 population

HCV in Multitransfused Children

- > 20 Egyptian studies ; 1993 through 2011 (mostly thalassemics)
- Maximum no studied <100
- Anti-HCV in 55-90% in early studies
- **HCV-RNA** dropped to **23-50%** in later studies
- One study showed decreased prevalence after 1993
- One study showed increased infection (15%) in neonates after exchange transfusion

Khalifa et al, J Trop Med Hyg, 1993
Mansour et al, Hematol Oncol Stem Cell Therap, 2012
El-Sayed et al, Egypt J Hematol, 2014
Mahmoud et al, Adv Hematol, 2016

HCV in Children with Hematological Malignancies

Three year prospective survey:

- Among 92 children receiving chemotherapy 62% were anti-HCV &/or HCV-RNA +ve (80% genotype 4)

(*El-Sayed et al, Hematol J 2003)*

- Prevalence and incidence is still high (high reservoir and burden of disease in an immune-suppressed population)

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Available online at www.sciencedirect.com

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Transplant Immunology 13 (2004) 305–311

Transplant Immunology

www.elsevier.com/locate/trim

Risk factors for cytomegalovirus, hepatitis B and C virus reactivation after bone marrow transplantation

Abdel-Rahman N. Zekri[a,*], Waleed S. Mohamed[a], Mohamed A. Samra[b], Ghada M. Sherif[c], Amal M.R. El-Shehaby[d], Manal H. El-Sayed[e]

European Journal of Gastroenterology & Hepatology 2004, 16:1347–1354

Liver disease is a major cause of mortality following allogeneic bone-marrow transplantation

Manal H. El-Sayed[a], Alaa El-Haddad[b], Omar A. Fahmy[c], Iman I. Salama[d] and Hossam K. Mahmoud[b]

Screening and Available Options

- Newborns of HCV mothers are screened for anti-HCV at 18 months
- *HCV-RNA* is indicated for screening of immunesuppressed children
- Validation of the Orasure Quick: testing *HCV in saliva* of high and low risk children (>98.5% sensitivity and specificity in immunecompromised children)

El-Sayed et al, Egypt J Hematol, 2014

- *Fibroscan*: cancer surviving adolescents with CHC (80% F3-F4).
- *APRI and FIB-4*: noninvasive alternatives for assessment of hepatic fibrosis differentiating mild from severe fibrosis (adolescents).

El-Sayed et al, Hepatology; 60 (S1): P681-530 A, 2014

Rationale to Treat HCV During Childhood

Clinical

- Higher SVR rate in older studies using conventional IFN
- Cost advantage using weight- and BSA-based dosing
- Relative absence of co-morbid factors
- Benefits of eradicating HCV before risky behaviors associated with transmission
- Better tolerance of medications (?)
- Excellent compliance with treatment
- *Treat Children with co-morbidities* to prevent relentless progression of liver disease

FDA Clears Two HCV Drugs for Children

- The US Food and Drug Administration (FDA) has approved the use of *sofosbuvir* and the combination of *ledipasvir and sofosbuvir* for hepatitis C virus (HCV) infection in children aged *12 and older* and weighing *at least 35 kg.*

April 7th 2017

C- Free Child

"Highlights"

Children and their families during awareness sessions

Board members during the awareness session

Training physicians on the program

Why HCV in Children?

Treatment

- Children better candidates
- Avoid disease progression
- Remove social stigma
- School performance and fatigue
- Extrahepatic manifestations and co-morbidities
- Decrease HCV burden and avoid transmission (CasP)-

Curing a patient saves ~ US$ 10,000 for the next 15 years Preventing a case saves ~ US$ 20,000 for the next 40 years.

Estes C, et al. Alim. Pharm. Ther. 2015

Treating Children with HCV
"Contraindications

- Activ… …hiatric disorder
- Pregnanc…
- Decompensated …
- Autoimmune diseases
- Renal dysfunction
- Active cancer
- Hemoglobinopathy
- Hemosiderosis

Not with DAAs

Infants-Young…
Neurological toxici…
Spontaneous viral clearance

Ongoing Trials in Adolescents and Children (Egypt)

- A Pilot Study for Safety and Efficacy of 12 Weeks *Sofosbuvir* Plus *Daclatasvir* with/without Ribavirin in Egyptian Adolescents with Chronic Hepatitis C Virus Infection (13 patients). (*Total number 50*)

  M. El-Sayed , EASL 2017,Abstract THU-412

- Safety and Efficacy of 12 Weeks Sofosbuvir/NS5A inhibitors with or without Ribavirin in Egyptian children (14-17 years old)with Chronic Hepatitis C Virus Infection

  M. El-Sayed , unpublished data

- Sof/Led in Adolescents and children undergoing chemotherapy for hematological malignancies (GS-US-337-1904) (Recruiting-ongoing)

Why HCV in Children?

Elimination

- Children are transmitters of HCV
- DAAs are safe and highly efficacious
- Cure as Prevention (CasP) before high risk behavior
- Globalisation (Immigration, migration, displaced children ….etc)
- Lack of screening policies for children and WoCBA
- Global elimination targets not achievable without inclusion of children

Challenges, Gaps and Future Outlook

- Research gaps
- Prevention of MTCT HCV (screening all pregnant women)
- Early treatment of women in CBA
- POC diagnostic tests
- Early treatment of children (consider extrahepatic manifestations, Psychiatric disorders and neurocongnitive dysfunction……)
- Pediatric clinical trials results and registration delayed
- Stigma
- Economics of manufacturing Pediatric formulations
- Access of children in low and LMIC to prevention and treatment

CRITICAL NEEDS

- Data a tabase networking
- Finance a elopment (*models financing R&D and production*)
- Eradicate HCV b dolescence (high risk behavior)
- Prioritise DAA lists fo in children
- Partnership with generic

-Pangenotypic

-Shortest duration

-No ribavirin

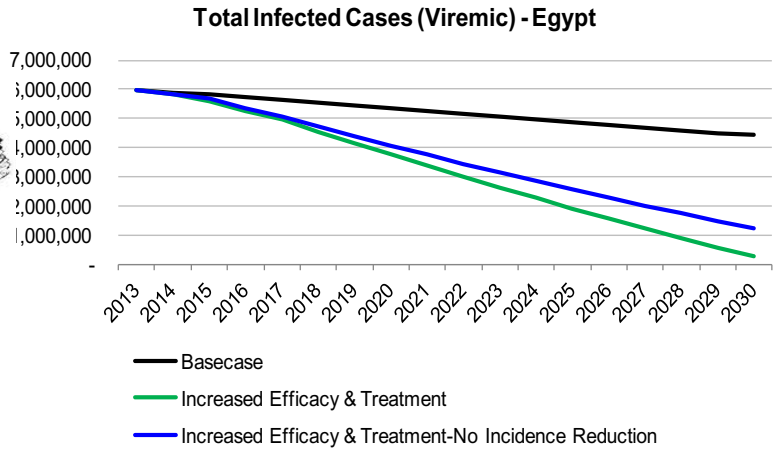
-Least adverse events

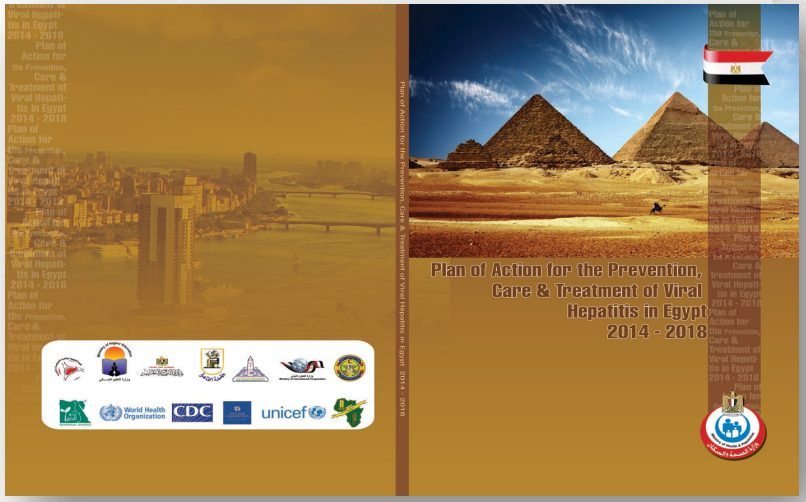
-Suitable for cirrhotics (+/- decompensated)

HCV in Children is CURABLE IN 12 WKS

Combining CasP and PasP

- Clinical trials with DAAs (GT4)
- Registration of Sofosbuvir 2014
- Web-based national patient enrolment for DAA treatment (>1.5 million so far)
- Treatment centers scaled up to 55
- Other DAAs introduced





	2014	2030	
Base Case	6,000,000	4,420,000	-26%
Increased treatment & SVR, reduce incidence		285,000	-95%
Increased treatment &SVR, without incidence reduction		1,250,000	-79%

Razavi et al, JVH, 2014
Waked et al, AJG, 2014

Key to Success

Diagnosis & Prevention

ACCESS

Care & Treatment

International Media

Acknowledgement

- The NCCVH members and chair: Prof Wahid Doss
- The Egyptian Liver Care Society board members and chair: Mrs Yosryia Sawiris
- Sawiris Foundation
- CIB Foundation
- WHO, US-CDC & Pasteur Institute *(development of national prevention plan)*

- *Pediatric Departments* at: **Ain Shams University**, National Liver Institutes in Cairo and Menoufia, Cairo University, Alexandria University, Mansoura University, Minia and Assiut Universities.
- *Pediatric Oncology and Virology Departments* at the National Cancer Institute and 57357 Hospital.
- *My patients and their families*

THANK YOU