“The Effectiveness of Treatment for Chronic Hepatitis C (and Hepatitis B) in Pediatric Populations”

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Disclosure

• Travel to three international meetings in 2015 and 2016 has been supported by pharma (Abbvie, Gilead and Quadri-Pharma)

• Member of Advisory board of Perspectum-Liver Multiscan

• Principal Investigator (\textit{PI}) in an Investigator Initiated Trial supported by Gilead Sciences for use of Harvoni in children and adolescents undergoing chemotherapy (\textit{PI} declined investigator fees to conduct the trial)
Why HCV & HBV in Children?

**Clinical Perspective**
- Infection mostly asymptomatic
- Children do not undergo biochemical testing or donate blood
- Many children with have normal ALT
- Risk factors are not known or sought
- Extrahepatic manifestations are rare
- Pediatricians do not consider the infection
- Progression of liver disease in high risk population groups

**Public Health Perspective**
- Children are transmitters of infection
- DAAs (HCV) are safe and highly efficacious
- Cure (HCV) or viral suppression (HBV) as Prevention (CasP) before high risk behavior in adolescence.
- Globalisation (Immigration, migration, displaced children ….etc)
- Lack of screening policies for children & WoCBA
- Global elimination targets not achievable without inclusion of children

**Elimination Goals**
Children at risk of HCV & HBV infection in LMIC?

- Undergoing recurrent blood or blood product transfusion or multiple invasive procedures (including circumcision and tattooing)
- Children born to infected mothers (up to 90% in HBeAg+ and 5-7% IN the HCV infected mothers)
- Children with an infected house-hold member
- Adolescents with high risk behavior

Prevalence in Children <15 yrs Egyptian National Surveys

- Data Excluding the High Risk Population Groups
- MOH Survey 2009: prevalence of HCV for 3678 Egyptian children from 1-15 yrs old in 8 representative Governorates (prevalence for HCV was 0.5%)
- DHS survey 2015: prevalence of 0.2-0.5% between ages 0 and 15 yrs (up to 0.8% in 15-19 yrs old)

- >10,000 are born yearly with HCV (DHS survey 2015: 7% HCV viremia among the Egyptian population (15-59 years)
During 2011–2014, increased HCV among WoCBA & children aged ≤ 2 years observed in the US and Kentucky (22% and 14%, nationally; >200% and 151%, Kentucky).

Birth certificate data showed the proportion of infants born to HCV-infected mothers increased 68% nationally and 124% in Kentucky.

Evaluates impact of substance abuse on pediatric HCV prevalence

From 2006 to 2012 nationally, the number of hospitalizations of children with HCV increased 37% (mean age 17.6 yrs)

HCV among 19-20 years of age represented 68% of the total HCV diagnoses (54% increase)

The burden was highest in whites, those in the lowest income quartile, and in the Northeast and Southern regions of the US.

The prevalence of substance use among children with HCV increased from 25% in 2006 to 41% in 2012
Natural History of HCV in Children

• Infections acquired during infancy are more likely to spontaneously resolve and fibrosis of the liver tends to increase with age.

• CHC acquired in childhood is associated with 26-fold increased risk of liver-related deaths.

• 50% acquiring HCV in early childhood are expected to clear the virus before the age of six.

• HIV co-infection increases the risk of vertical transmission and progression of liver disease.

• Co-morbidities including siderosis, cancer chemotherapy among others increase the risk of progression of liver disease.
Treatment of children with co-morbidities

32/36 patients underwent liver biopsy, macrovesicular hepatic steatosis associated with chronic hepatitis C was documented in 10 children (31.3%).

BMI was higher (P ≤ 0.05) and apo-B was lower in steatotic (P ≤ 0.05) than non-steatotic HCV-infected children.

ALT and apo-B were independent predictors for hepatic steatosis (P<0.001, and <0.05, respectively).

Worse response to Peg-interferon alpha 2-b plus ribavrin treatment for HCV was reported among children with steatosis (P < .001).

Lipid profile and Hepatic Steatosis in HCV infected Cancer Survivors

Positive Univariate Correlation between fibrosis stage and ALT Flares in children under cancer chemotherapy

El-Sayed et al, Hepatology 54; S1:715, 2011.

Al-Tawil et al, Pediatr Hematol Oncol, 2015
Hepatitis B
Natural History in Children

- Infected neonates usually asymptomatic, small % fulminant hepatitis
- Giannotti-Crosti Syndrome
  - Infants >6 months – young children
    - Papular acrodermatitis for weeks
    - Mild fever and lymphadenopathy
    - Anicteric
  - Older children – adolescents
    - mild constitutional symptoms
    - fulminant hepatitis

- Extrahepatic manifestations…
  - Membranous glomerulonephritis
- ? Rapid progression in % children
  - Cirrhosis / HCC (1-3% cirrhotic at presentation
    HCC: 1/1000/yr (?)
- Spontaneous clearance of HBeAg / HBV DNA commoner in Western children – ie. lower in Asian suggesting genetic differences in background of immune response*
- 4 TO 10 % annual HBe Ag - Ab seroconversion (< 2% if < 3ys), up to 70% end of adolescence
- 0 to 1% annual HBs Ag -Ab seroconversion
- Perinatal infection ➔ inability to clear HBsAg (asian)
- More active disease beyond adolescence
- More favourable evolution in female, genotype B

Chronic hepatitis B virus (HBV) infection in children: 25 years’ experience

C. Popalis,1,2 L. T. F. Yeung,1,2,3,4 S. C. Ling,1,2 V. Ng1,2 and E. A. Roberts1,2,5,6 1Division of Gastroenterology, Hepatology and Nutrition, Hospital for Sick Children, Toronto, ON, Canada; 2Department of Paediatrics, University of Toronto, Toronto, ON, Canada; 3Rouge Valley Health System, Toronto, ON, Canada; 4Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, ON, Canada; 5Departments of Medicine; and 6Pharmacology, University of Toronto, Toronto, ON, Canada

Received June 2012; accepted for publication September 2012

- Of 252 HBeAg-positive cases, 59.9% had HBV-infected mothers, 77% were Asian, and 33 received interferon-α.
- e-seroconversion rate was 41.7% over 0.5–19.1 years of follow-up
- 49% achieved inactive chronic infection by age 19 years.
- Being non-Asian, age at diagnosis < 3 years, and ALT ≥40 IU/mL were associated with a higher rate of e-seroconversion
Treatment Recommendations in Children:
Antiviral therapy in HBeAg+ve children (2 to <18 years) with both elevated ALT and measurable HBV DNA, with the goal of achieving sustained HBeAg seroconversion

- ALT elevation (>1.3 times ULN) at least 6 mths with HBV DNA elevations.
- HBV DNA levels are very high during childhood (>10^6 IU/mL)
- If a level <10^4 IU/mL is observed, therapy might be deferred until other causes of liver disease and spontaneous HBeAg seroconversion are excluded.
- Interferon-a-2b is approved for children 1 year of age and older, whereas lamivudine and entecavir are approved for children 2 years of age and older.
- Tenofovir is approved for children 12 years of age and older.
- Duration of treatment with interferon-a-2b is 24 weeks.
- Duration of treatment with oral antivirals that has been studied is 1-4 years.
- Use HBeAg seroconversion as a therapeutic endpoint when oral antivirals are used, continuing treatment for an additional 12 months of consolidation, as recommended in adults.
- Children who stop antiviral therapy should be monitored every 3 months for at least 1 year for recurrent viremia, ALT flares, and clinical decompensation.
Control of HCV and HBV In Children

**Prevention as Prevention**
- Strengthening surveillance to detect viral transmission and disease (acute and chronic)
- Promoting Infection Control Practices
- Improving blood safety
- Eliminating Transmission through universal HB birth dose implementation
- Prevention of MTCT
- Educating providers and communities to reduce transmission of viral hepatitis
- Raising awareness and development of special engaging programs for children
- Research Agenda for gaps in this key population

**Treatment as Prevention**
- **Cure** as prevention of transmission (HCV)
- Viral **suppression** as prevention of transmission (HBV)
- Prevention of **progression** of liver disease
- Prevention of **neurocognitive** dysfunction
- Prevention of **stigma** and discrimination
- Prevention of **reactivation** in the immunocompromised populations
- Prevention of **transmission** in high risk populations
- Prevention of **MTCT**
Approved but not Accessible!

HBV:
Entecavir for children 2 years and above
Tenofovir for children 12 years and above

HCV:
7th April 2017 FDA approved Sofosbuvir and Sofosbuvir plus Ledipasvir for children 12 years and above and weighting >35 kg
EMA approved the same combination June 2017
Trials for smaller children--------undergoing
Emtricitabine/Tenofovir Alafenamide (FTAF) in HIV-1 Infected Children an Adolescents Virologically Suppressing a 2-NRTI-Containing Regimen

This study is currently recruiting participants.

See contacts and locations

Verified November 2017 by Gilead Sciences

Sponsor:
Gilead Sciences

ClinicalTrials.gov Identifier:
NCT02285114

First Posted: November 6, 2014
Last Update Posted: November 17, 2014

Tenofovir Alafenamide (TAF) Adolescents With Chronic H Virus Infection

See contacts and locations

Verified November 2017 by Gilead Sciences

Sponsor:
Gilead Sciences

ClinicalTrials.gov Identifier:
NCT02932150

First Posted: October 13, 2014
Last Update Posted: October 13, 2014

A Phase III Study of the Safety and Efficacy of Entecavir in Pediatric With Chronic Hepatitis B Virus (HBV) Infection

This study is ongoing, but not recruiting.

Sponsor:
Bristol-Myers Squibb

ClinicalTrials.gov Identifier:
NCT01079806

First Posted: March 3, 2011
Last Update Posted: March 3, 2011

Entecavir/Pegylated Interferon in Immune Tolerant Children With Chronic Hepatitis B Virus (HBV) Infection

This study has been completed.

Sponsor:
National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

ClinicalTrials.gov Identifier:
NCT01368497

First Posted: June 8, 2011
Last Update Posted: August 25, 2017
Ongoing paediatric trials of direct acting antivirals regimens for hepatitis C virus mono-infected, treatment-naïve and –experienced children aged 3 to 17 years

- Led/Sof (FDC) ± RIB (NCT02249182), G 1; 4; 5; 6; 3* (3-17 yrs), recruiting
- Sof+RIB (NC02175758), G 2; 3 , 3-17 yrs, Active not recruiting
- OBV/PPTV/RTV ± DSV ± RIB (NCT02486406) , G 1;4 (3-17 yrs), recruiting
- Glecaprevir/Pibrentasvir (NCT03067129) , G 1-6, 3-17 yrs, recruiting
- Sofosbuvir/Velpatasvir (NCT 03022981) , G 1-6, 3-17 yrs, recruiting
Ongoing Trials in Adolescents & 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 (12-18 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), G 1;4 (Recruiting-ongoing-total number 40)

- **Sof/Ravi** in adolescents and children, 3-17 yrs, G 1-6 (recruiting-total number 150)
Interim results for NS5A based DAA therapy in 12-18 yrs SVR 12 in 37 patients

MH El-Sayed, EASL 2017, Abstract THU-412

MH El-Sayed, unpublished data
Shortened 8 Weeks Course of Dual Sofosbuvir/Daclatasvir Therapy in Adolescent Patients, with Chronic Hepatitis C Infection

- A pilot single cohort of 10 consecutive adolescents with chronic HCV
- Treated with dual (SOF/DCV) therapy for a response-tailored duration of 8 weeks for those who achieved very rapid virologic response (vRVR) and 12 weeks for those who did not.
- All patients achieved vRVR at week 2 and completed the shortened 8 weeks course.
- All patients (10/10 (100% (CI: 72.25–100%)) achieved SVR12 with good tolerability and no serious adverse events.

Ledipasvir/Sofosbuvir ± Ribavirin for 12 or 24 Weeks Is Safe and Effective in Children 6–11 years old with Chronic Hepatitis C Infection

Results: Adverse Events (≥ 10% in LDV/SOF Week Group)
LDV/SOF in Children 6 to 11 years old

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>LDV/SOF 12 Weeks n=87</th>
<th>LDV/SOF 24 Weeks n=1</th>
<th>LDV/SOF + RBV 24 Weeks n=2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>16 (18)</td>
<td>0</td>
<td>1 (50)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>14 (16)</td>
<td>0</td>
<td>1 (50)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>13 (15)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12 (14)</td>
<td>0</td>
<td>1 (50)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12 (14)</td>
<td>1 (100)</td>
<td>1 (50)</td>
</tr>
<tr>
<td>Cough</td>
<td>11 (13)</td>
<td>0</td>
<td>1 (50)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10 (11)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>9 (10)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>9 (10)</td>
<td>0</td>
<td>1 (50)</td>
</tr>
</tbody>
</table>

LDV/SOF 45/200 mg

Results: SVR12
LDV/SOF in Children 6 to 11 years

- 99
- 100
- 100

1 GT1a patient with cirrhosis relapsed at Follow up 4 visit

Error bars represent 90% confidence interval. LDV/SOF 45/200 mg
Prevention of MTCT-HBV and HCV

HBV and HCV

- Preterm birth
- Low birth weight
- Premature rupture of membranes

HBV:
- Neonatal "vaccination" and "immunoprophylaxis," antiviral agents such as TDF or telbivudine during pregnancy beginning at 32 wks of gestation is safe and effective in preventing MTCT.

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.
- HCV MTCT can be minimized by avoiding *fetal scalp electrodes and *birth trauma.
- Young women with HCV should be referred for treatment post delivery, and neonates should be closely followed to rule out infection.
Role of Civil Society

Free-C Child Project

- **ECLS**, Sawiris and CIB Foundations under supervision of NCCVH (cost 10 million LE=0.5-1 million USD)
- Screened 3050, 9 treatment centers in University and teaching hospitals
- 933 children and adolescents (3-18 yrs) have been included since 2010.
- All received “Peg-interferon” plus “ribavirin”
- Training HCWs in each individual center
- Support clinical, laboratory and radiological work-up through the whole project
- Developed central database
- Awareness sessions for children and their families
- Distribution of personal care items (5 times during the period of treatment)
- Nutritional support

![Meeting with children and families](image1.jpg)

![Chart showing treatment outcomes](chart.jpg)
Why Treat HCV and HBV in Children?

**Clinical Perspective**

- Cost advantage using weight-based dosing
- Relative absence of co-morbid factors
- Benefits of eradicating HCV and suppressing HBV 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

**Treatment Perspective**

- 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.

Improve Quality of Life
Challenges and Gaps

- Research gaps
- Prevention of MTCT (screening all pregnant women)
- Early treatment of women in CBA
- POC diagnostic tests!
- Early treatment of children (consider extrahepatic manifestations, Psychiatric disorders and neurocognitive 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
- Engage the family
- Service delivery programs particularly for adolescents

Increased HCV testing of pregnant women, testing guidelines for children born to HCV-Infected women, and subsequent linkage of mother and infant to care and treatment to prevent HCV-related sequelae.
Critical Needs

- Data and database networking
- Finance & R&D development (models financing R&D and production)
- Eradicate HCV before adolescence (high risk behavior)
- Prioritise DAA lists for HCV in children
- Partnership with generics
  - Pangenotypic
  - Shortest duration
  - No ribavirin
  - Least adverse events
  - Suitable for cirrhotics (+/- decompensated)

Clinical trials are urgently needed to address the HBV immunotolerant Pediatric population
Service delivery issues in adolescents and children

- **Age of consent**
  Legal, policy and ethical barriers limit access to services for adolescents and data collection especially 10-14 year olds

- **Disclosure and Stigma**
  Adolescents may need particular support with disclosure. May need to engage support of family members and teachers

- **Access:**
  How to access adolescents – most are either at home or in schools – environments that are often not easy to access

- **Cultural and social barriers**
  Sexual issues sometimes considered taboo and socially inappropriate to discuss with adolescents
MAJOR GAPS IN VIRAL HEPATITIS CARE

TESTING GAP

HEPATITIS B
(% OF PEOPLE DIAGNOSED)

2015 BASELINE | 2020 TARGETS | 2030 TARGETS FOR ELIMINATION

9% | 20% | 90%

HEPATITIS C
(% OF DIAGNOSED PEOPLE ON CURE)

2015 BASELINE | 2030 TARGETS FOR ELIMINATION

7% | 80%

Proritise Children, Adolescents and WoCBA within the cascade of viral hepatitis care and treatment.
Acknowledgement

- NCCVH
- Egyptian Liver Care Society
- National Cancer Institute in Cairo
- 57357 Children’s Cancer Hospital
- Faculty of Medicine Ain Shams University Clinical Research Institute (MASRI)
- Patients and their Families
- All supportive individual donors and foundations (Sawiris, CIB, EFG Hermes)