XI Workshop Nazionale

Innovazione e Ricerca per la Pratica Clinica

TERAPIE INNOVATIVE DELLE EPATITI CRONICHE VIRALI E DELLE INFEZIONI VIRALI

Firenze, 11-12 Gennaio 2021

VIRTUAL EDITION

Update sul paziente pediatrico

Firenze, 11 gennaio 2020

Giuseppe Indolfi

UNIVERSITÀ DEGLI STUDI FIRENZE

Penta Child Health Research

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Direct-Active Antivirals Approvals (Jan 2021)

- **Sofosbuvir + ribavirin** – **3-17 years of age**
- **Sofosbuvir/ledipasvir(FDC)** – **3-17 years of age**
- **Glecaprevir/pibrentasvir(FDC)** – **12-17 years of age**
  – **3-11 years expected June 2021**
- **Sofosbuvir/velpatasvir(FDC)** – **6-17 years of age**
  – **3-5 years expected June 2021**

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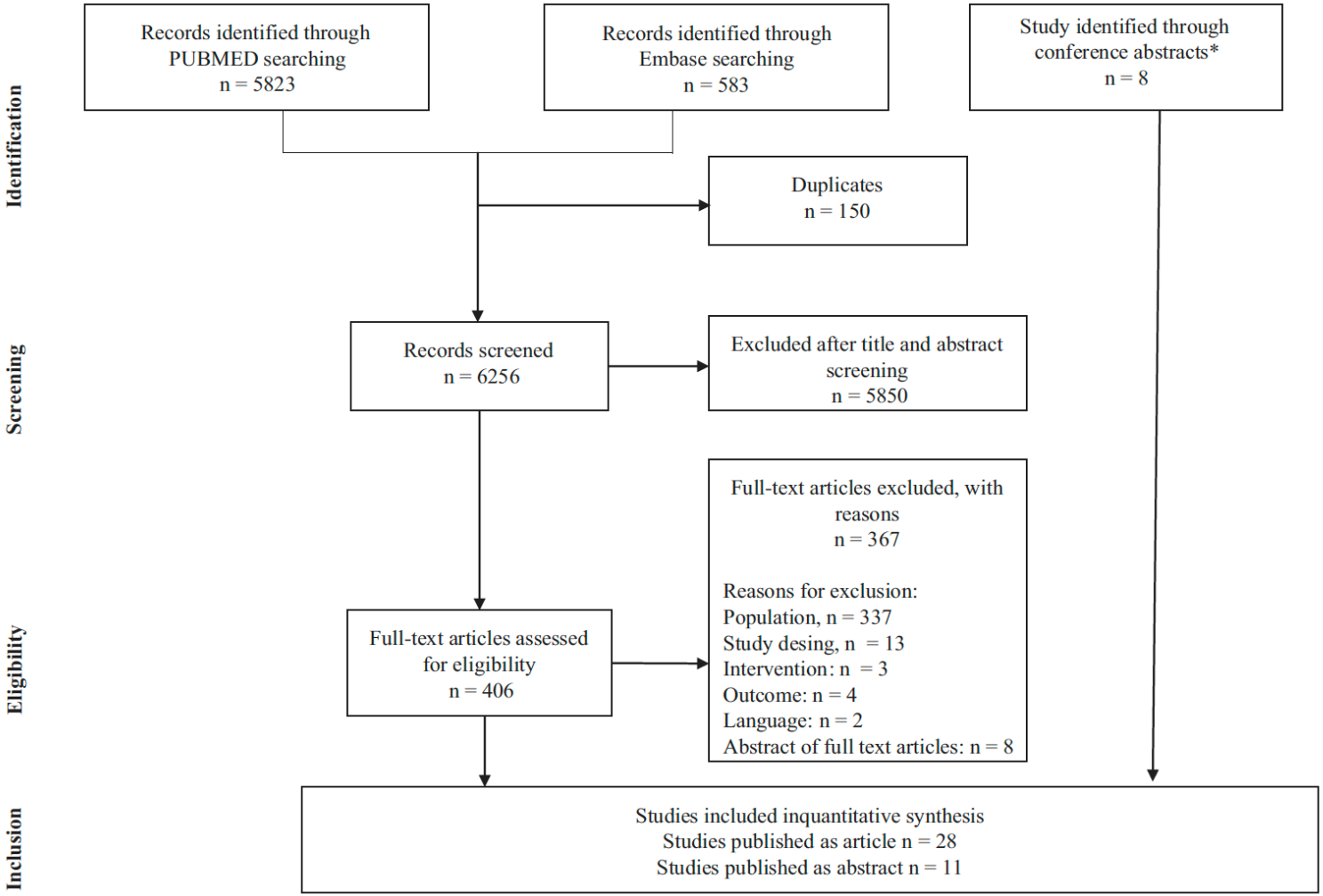
Systematic Review with Meta-Analysis
DAA for Children and Adolescents with CHC



Indolfi G, Aliment Pharmacol Ther 2020

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Meta-analysis of Proportions
DAA for Children and Adolescents with CHC

$$\frac{\text{subjects } \textbf{achieving} \text{ SVR12}}{\text{subjects receiving } \textbf{all doses of treatment}} \qquad \frac{\textbf{subjects achieving SVR12}}{\textbf{subjects receiving at least one dose}}$$

- **Age of the patients (3-5; 6-11; 12-17 years)**
- **Presence of cirrhosis**
- **Treatment duration (8; 12; 24 weeks)**
- **Treatment type**
- **Previous history of treatment**

Indolfi G, Aliment Pharmacol Ther 2020

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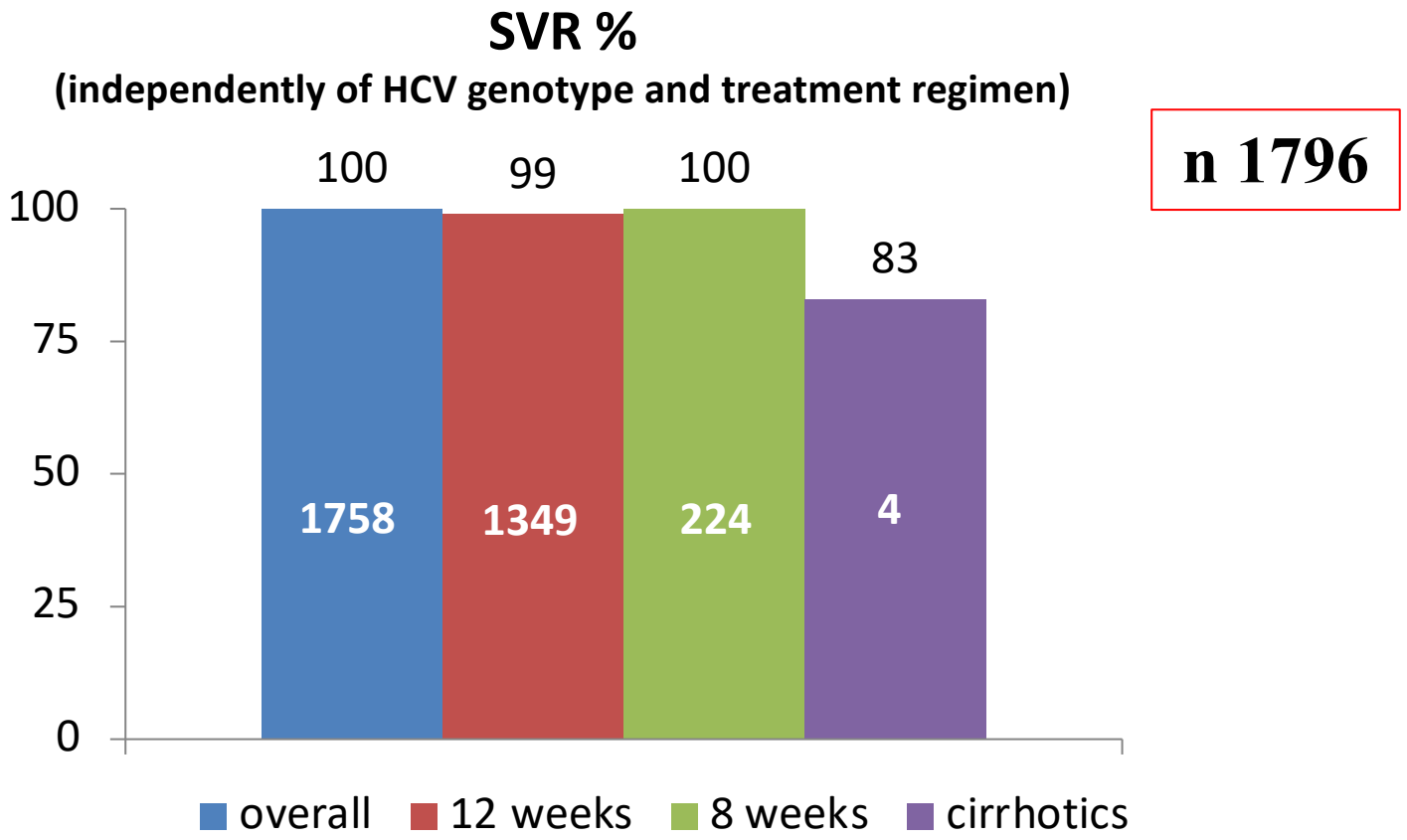
Meta-analysis of Proportions
DAA for Children and Adolescents with CHC



n 1796

Indolfi G, Aliment Pharmacol Ther 2020

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Meta-analysis of Proportions
DAA for Children and Adolescents with CHC

	No. of study-arms pts reaching SVR12 / pts receiving all doses of treatment	Proportion [95% CI]	No. of study-arms pts reaching SVR12 / pts receiving at least one dose of treatment	Proportion [95% CI]
Overall	60 (1758/1772)	100 [100-100]	42 (1340/1403)	99.9 [98.7-100]
Duration of treatment				
8 weeks	7 (224/224)	100 [99.6-100]	6 (181/182)	100 [98.6-100]
12 weeks	40 (1349/1356)	100 [100-100]	25 (967/992)	99.5 [98.5-100]
16-24 weeks	12 (165/170)	100 [100-100]	9 (116/119)	100 [100-100]
I^2 statistic, p-value[d]		(0.03)		(0.08)
Drug				
EBR + GZR	3 (37/37)	100 [95.4-100]	-	-
GLC + PIB	2 (47/47)	100 [99.6-100]	2 (47/47)	100 [99.6-100]
OBV + others	4 (38/38)	100 [99.1-100]	4 (38/38)	100 [99.1-100]
SOF + others	51 (1636/1650)	100 [100-100]	36 (1255/1318)	99.6 [97.7-100]
I^2 statistic, p-value[d]		(0.95)		(0.37)
Inclusion of cirrhotic patients				
No	37 (1157/1164)	100 [100-100]	28 (1030/1087)	99.2 [96.7-100]
Yes	5 (9/9)	100 [78.1-100]	3 (3/4)	83.0 [18.5-100]
I^2 statistic, p-value[d]		(0.34)		(0.11)
Previous history of treatment				
Non-naïve to therapy patients	3 (157/157)	100 [100-100]	3 (157/160)	100 [98.4-100]
Naïve to therapy patients	38 (1247/1259)	100 [100-100]	30 (969/995)	99.7 [98.8-100]
I^2 statistic, p-value		(0.34)		(0.62)
Age (range)				
3-5 years	6 (74/74)	100 [98.2-100]	5 (67/69)	99.2 [93.7-100]
≥6 years	46 (1268/1275)	100 [100-100]	32 (913/958)	100 [98.6-100]
I^2 statistic, p-value		(0.94)		(0.89)

Indolfi G, Aliment Pharmacol Ther 2020

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Meta-analysis of Proportions
DAA for Children and Adolescents with CHC

Adverse event	Main analysis[b]		
	No. of study-arms (No. of pts with Adverse events/no. of pts receiving at least one dose of treatment)	Proportion [95% CI]	Heterogeneity between studies, I^2 statistic (*P*-value[c])
Headache	24 (287/1126)	19.9 [12.7-28.0]	89.2 (<0.001)
Fatigue/asthenia	25 (215/1144)	13.9 [7.1-22.3]	91.8 (<0.001)
Nausea	24 (123/1126)	8.1 [3.5-14.0]	88.5 (<0.001)
Abdominal pain	25 (136/1144)	7.0 [2.0-14.1]	92.5 (<0.001)
Diarrhoea	24 (120/1126)	4.8 [1.4-9.7]	87.7 (<0.001)
Cough	24 (96/1126)	4.0 [0.8-9.0]	89.3 (<0.001)
Vomiting	25 (73/1144)	2.6 [0-6.3]	86.0 (<0.001)
Serious adverse events	27 (3/1350)	0 [0-0.001]	0.0 (1.0)

Indolfi G, Aliment Pharmacol Ther 2020

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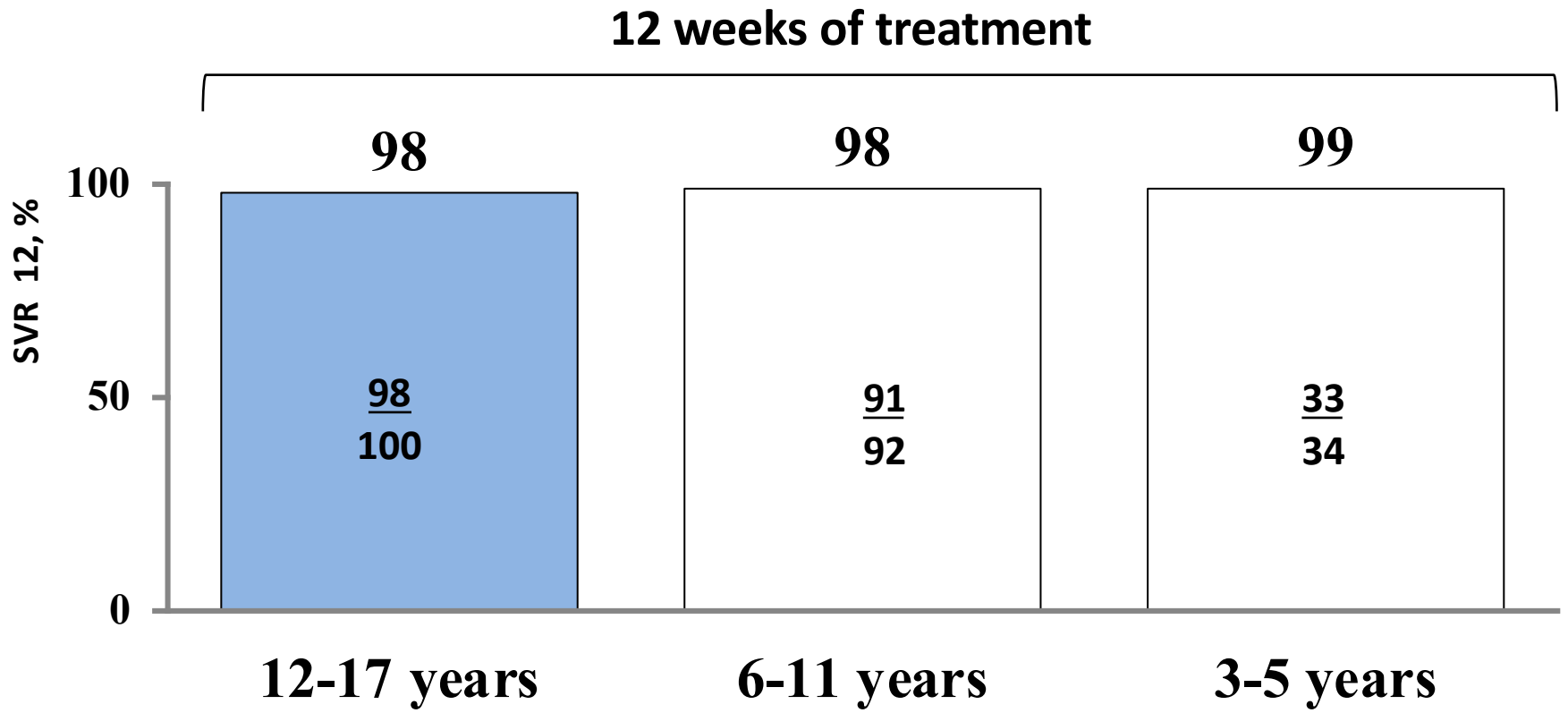
Sofosbuvir(nNS5B) / ledipasvir(NS5A) (FDC)

NCT 02249182, industry-driven trial

EMA FDA



Sofosbuvir/ledipasvir
12-17 years:400/90 mg QD FDC; 6-11 years: 200/45 mg QD FDC (tabs 22.5/100 mg);
3-5 years AND ≥ 17 Kg 200/45 mg (granules) QD; AND < 17 Kg: 150/33.75 mg QD (granules)

Balistreri WF, Hepatology 2017
Murray K, Hepatology 2018
Schwarz KB, Hepatology 2020

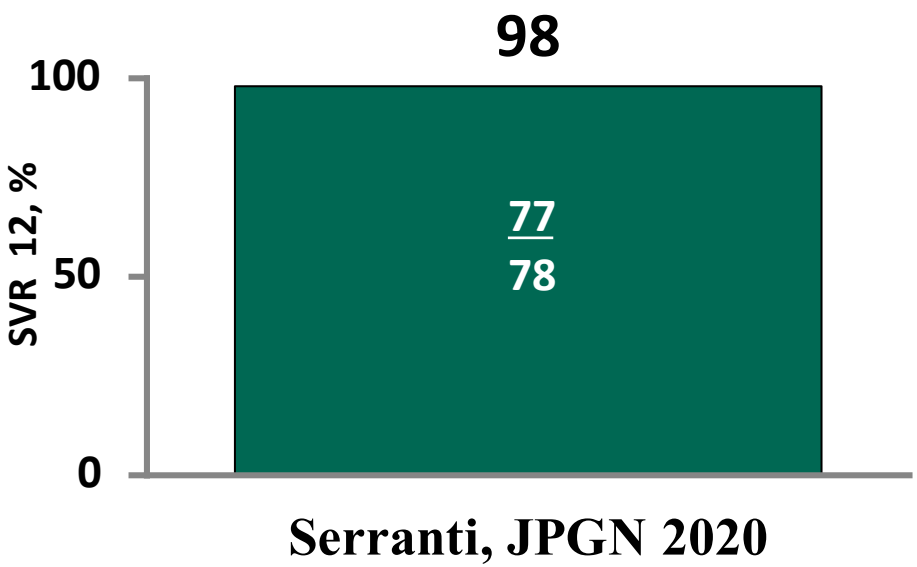
Sofosbuvir(nNS5B) / ledipasvir(NS5A) (FDC)

Real-world data – The CIAO-C Study

EMA FDA

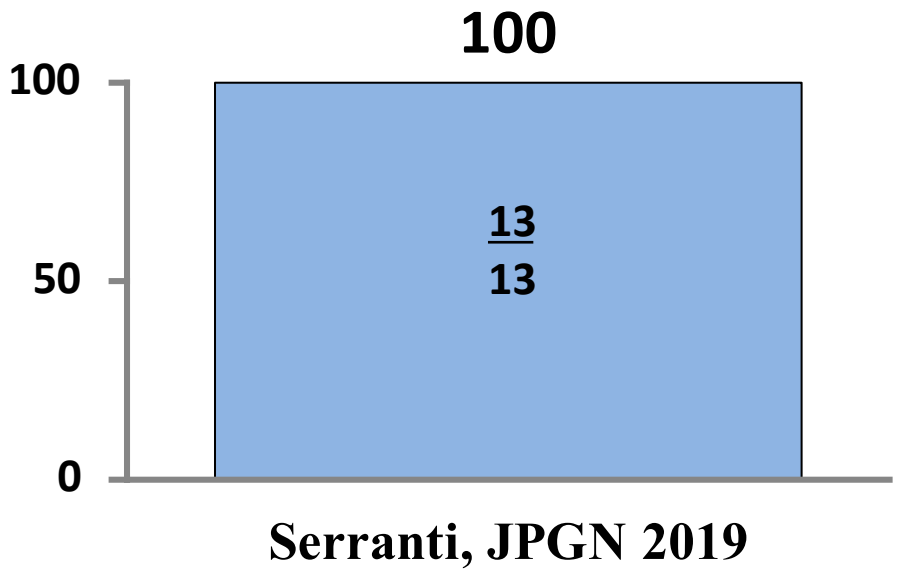
12-17 years, GT1, 3, 4, (n 13)

8-12 weeks of treatment



12-17 years, GT1, treatment-naïve, HCV RNA < $6x10^6$ IU/mL (n 13)

8 weeks of treatment

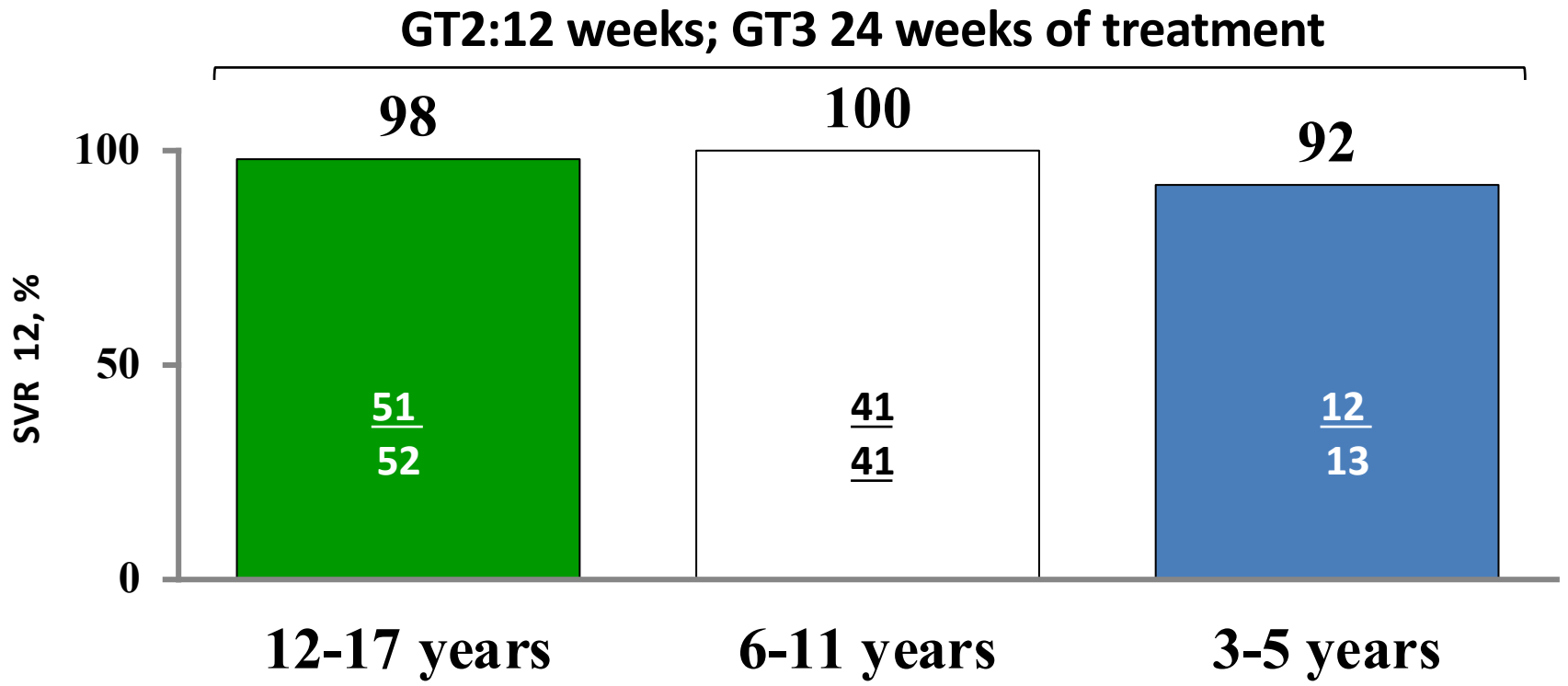


Sofosbuvir/ledipasvir (400/90 mg QD) FDC

Sofosbuvir$_{(nNS5B)}$ + ribavirin

NCT 02175758, industry-drive trial

EMA FDA



Ribavirin weight-based
Sofosbuvir 12-17 years: 400 mg QD tablet; 6-11 years 200 mg tablet;
3-5 years and: ≥ 17 kg: 200 mg (granules); <17 kg: 150 mg (granules)

Wirth, Hepatology 2017
Rosenthal P, Hepatology 2020

Sofosbuvir(NS5B) / velpatasvir(NS5A) (FDC)

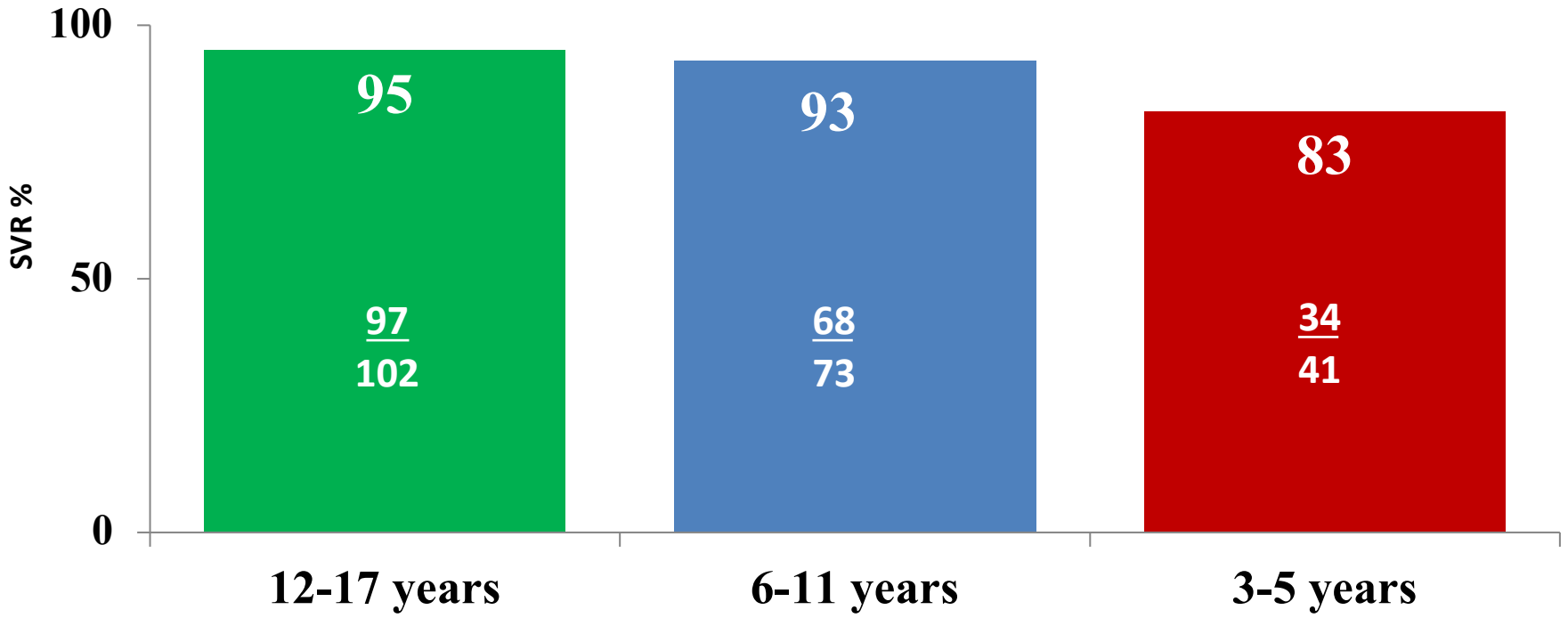
NCT 03022981, industry-driven trial

EMA FDA

6-17 years

3-17 years, HCV GT1-6, cirrhotic and non-cirrhotic

12 weeks (12-18 years: n 102; 6-11 years: n 73; 3-5 years: n 41)



12-17 years: 400/100 mg QD (tablets)
6-11 years: 200/50 mg QD (tablets or oral granules),
3-5 years: >17 Kg: 200/50 mg; <17 Kg 150/37.5 mg, QD (oral granules)

Jonas MM, AASLD 2019 and 2020
Clinicaltrial.gov

Sofosbuvir(NS5B) / velpatasvir(NS5A) (FDC)

NCT 03022981, industry-driven trial

EMA FDA

6-17 years

3-17 years, HCV GT1-6, cirrhotic and non-cirrhotic

	12-18 years	6-11 years	3-5 years
n	102	73	41
Virological failure	1	1	0
Lost to follow up	6	2	1
Non compliance with study drug	0	0	2
Investigator's discretion	0	1	2
Withdrew Assent By Parent/Guardian	0	0	1

12-17 years: 400/100 mg QD (tablets)
6-11 years: 200/50 mg QD (tablets or oral granules),
3-5 years: >17 Kg: 200/50 mg; <17 Kg 150/37.5 mg, QD (oral granules)

Jonas MM, AASLD 2019 and 2020
Clinicaltrial.gov

Glecaprevir(PI) / pibrentasvir(NS5A) (FDC)

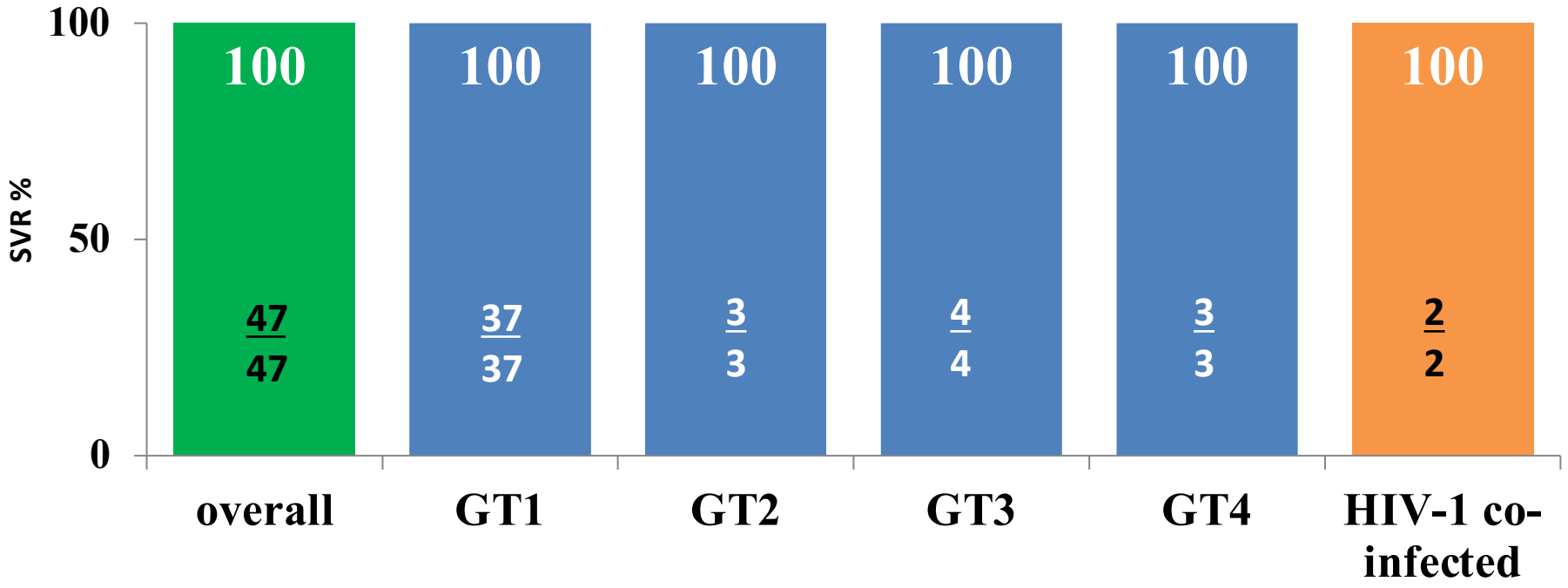
NCT 03067129, industry-drive trial

EMA FDA

12-17 years, HCV GT1-6, cirrhotic and non-cirrhotic, ± HIV co-infection

DORA part 1

non-cirrhotics 8 weeks (n 44); compensated cirrhosis 12 weeks (n 0); GT3 exp 16 weeks



Glecaprevir/pibrentasvir (300/120 mg QD), FDC (100/40 mg)

Jonas MM, Hepatology 2020

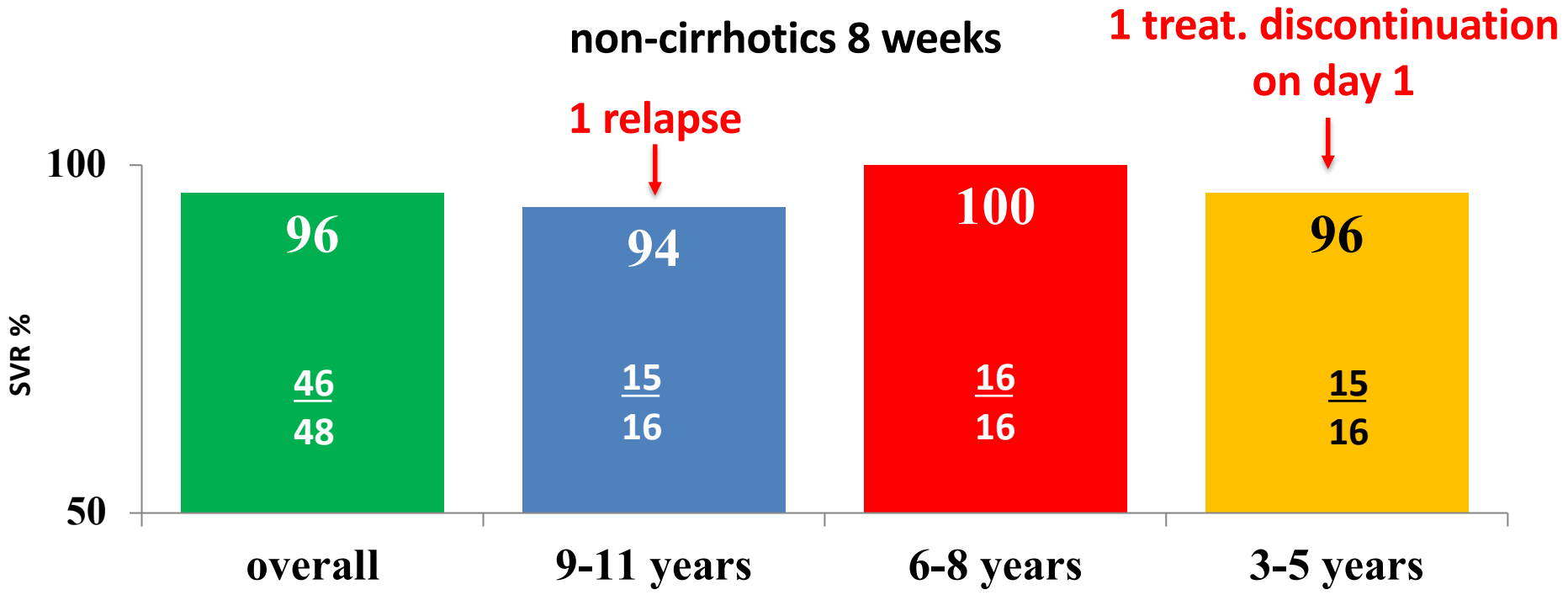
Glecaprevir(PI) / pibrentasvir(NS5A) (FDC)

NCT 03067129, industry-drive trial

EMA FDA

3-11 years, HCV GT1-6, cirrhotic and non-cirrhotic

DORA part 2



Glecaprevir/pibrentasvir film coated granules
9-11 years - 30 to < 45 Kg: 250/100 mg QD
6-8 years - 20 to < 30 Kg: 200/80 mg QD
3-5 years - 12 to < 20 Kg: 150/60 mg QD

Jonas MM, AASLD 2019

Monitoring of Treatment with DAA in Children

Baseline
Clinical assessment
Laboratory tests: hepatic and renal function panel, complete blood count, hepatitis B virus serology, hepatitis B surface antigen, quantitative HCV RNA, HCV genotype

↓

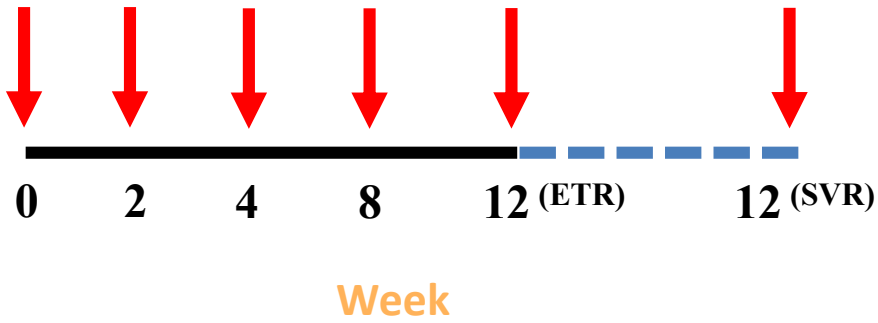
Treatment week 2 or 4
(adherence check)
Quantitative HCV RNA

↓

Every 4 weeks from baseline
Clinical assessment
Assessment of adverse events
Laboratory tests (alanine aminotransferase, renal function, complete blood count)

↓

End of treatment and 12 weeks after
(efficacy)
HCV RNA



ETR, end of treatment response; SVR sustained virological response

Indolfi, Lancet Child & Adolesc Health 2018

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Telemedicine for HCV Treatment in Children

	Baseline Mean (SD)	EoT Mean (SD)	Δ %
Haemoglobin g/dL	14,4 (1,2)	14,2 (1,4)	**-1,0**
Creatinine mg/dL	0,68 (0,14)	0,68 (0,15)	**+0,8**
Urea mg/dL	27 (6,5)	25,5 (6,4)	**-5,8**

	Baseline Median (IQR)	EoT Median (IQR)	Δ %
Bilirubin tot mg/dL	0,63 (0,5-0,85)	0,6 (0,4-0,9)	**-4,8**
Albumin g/dL	4,5 (4,2-4,7)	4,4 (4,3-4,7)	**-2,2**
WBC/mm^3	6120 (5230-6970)	6425 (5630-7455)	**+5**
PLT x10^6/mm^3	248 (207-289)	252 (216-287)	**+1,6**

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Monitoring of Treatment with DAA in Children

Baseline
Clinical assessment
Laboratory tests: hepatic and renal function panel, complete blood count, hepatitis B virus serology, hepatitis B surface antigen, quantitative HCV RNA, HCV genotype

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Treatment week 2 or 4
(adherence check)
Quantitative HCV RNA

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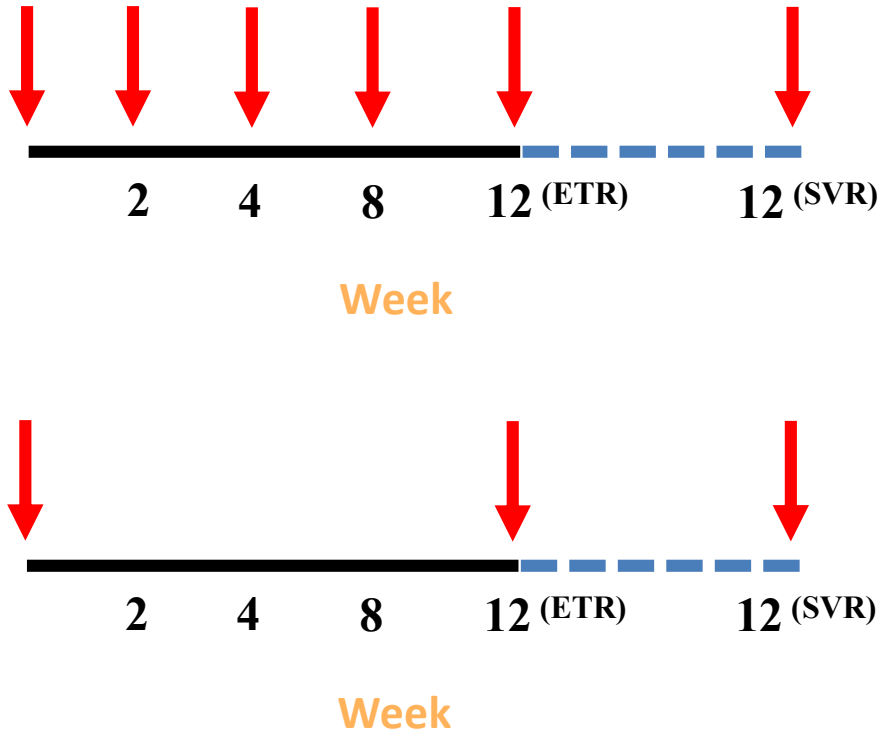
Every 4 weeks from baseline
Clinical assessment
Assessment of adverse events
Laboratory tests (alanine aminotransferase, renal function, complete blood count)

↓

End of treatment and 12 weeks after
(efficacy)
HCV RNA



ETR, end of treatment response; SVR sustained virological response

Indolfi, Lancet Child & Adolesc Health 2018

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Indications for Treatment of chronic HCV

Natural history of the infection

Comparison of the AASLD, WHO, EASL, ESPGHAN, APASL guidelines: a FISPGHAN position paper

- There is agreement towards:

  - treatment of all the adolescents (12-17 years of age)
  - deferral of treatment in younger children (between 3 and 11 years of age) until DAA combinations are available
  - none of the selected documents reported any specific consideration on treatment of children younger than 3 years of age

Indolfi G, J Ped Gastroenterol Hepatol 2020

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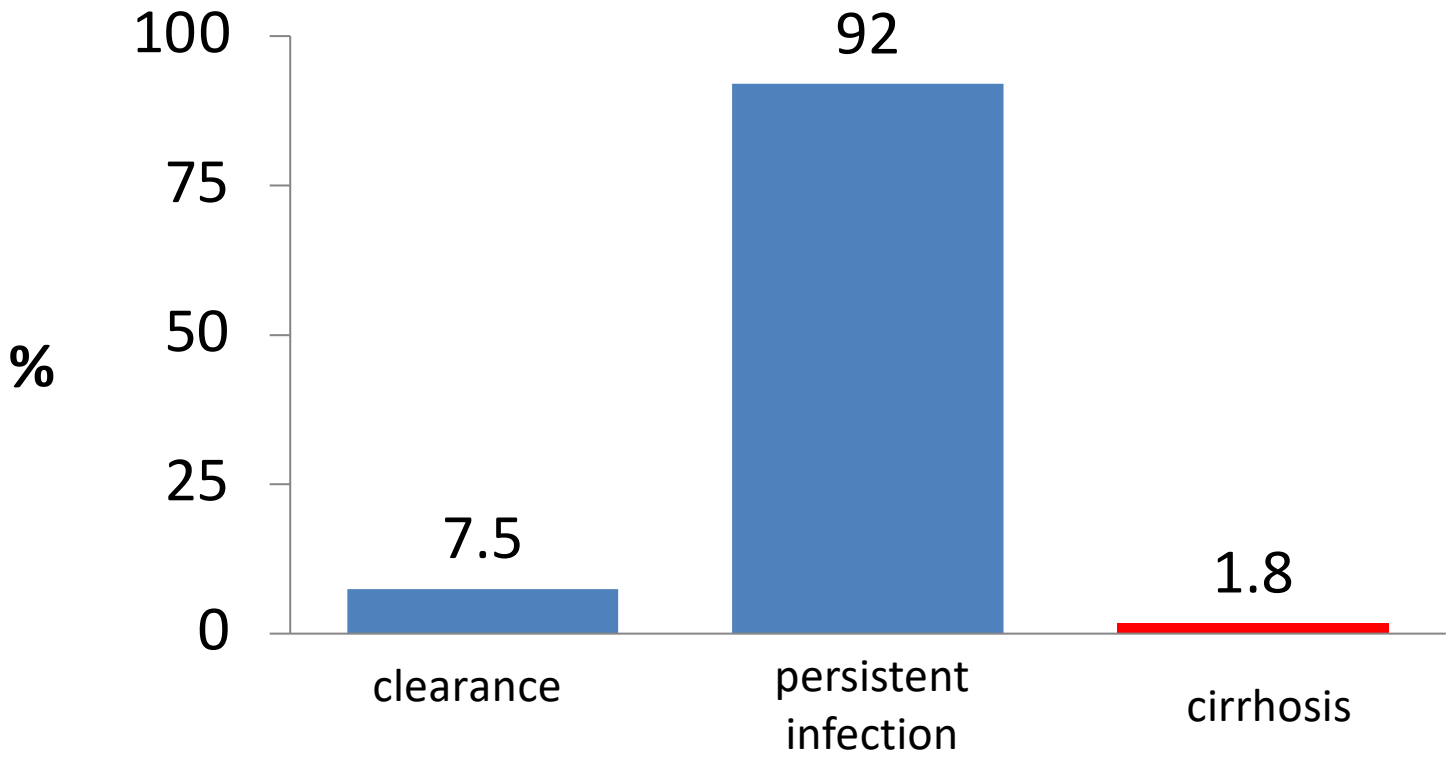
Hepatitis C in Children

Natural history of the infection

- **504 children with hepatitis C**
- **follow up: 10 years**



Bortolotti F, Gastroenterology 2008

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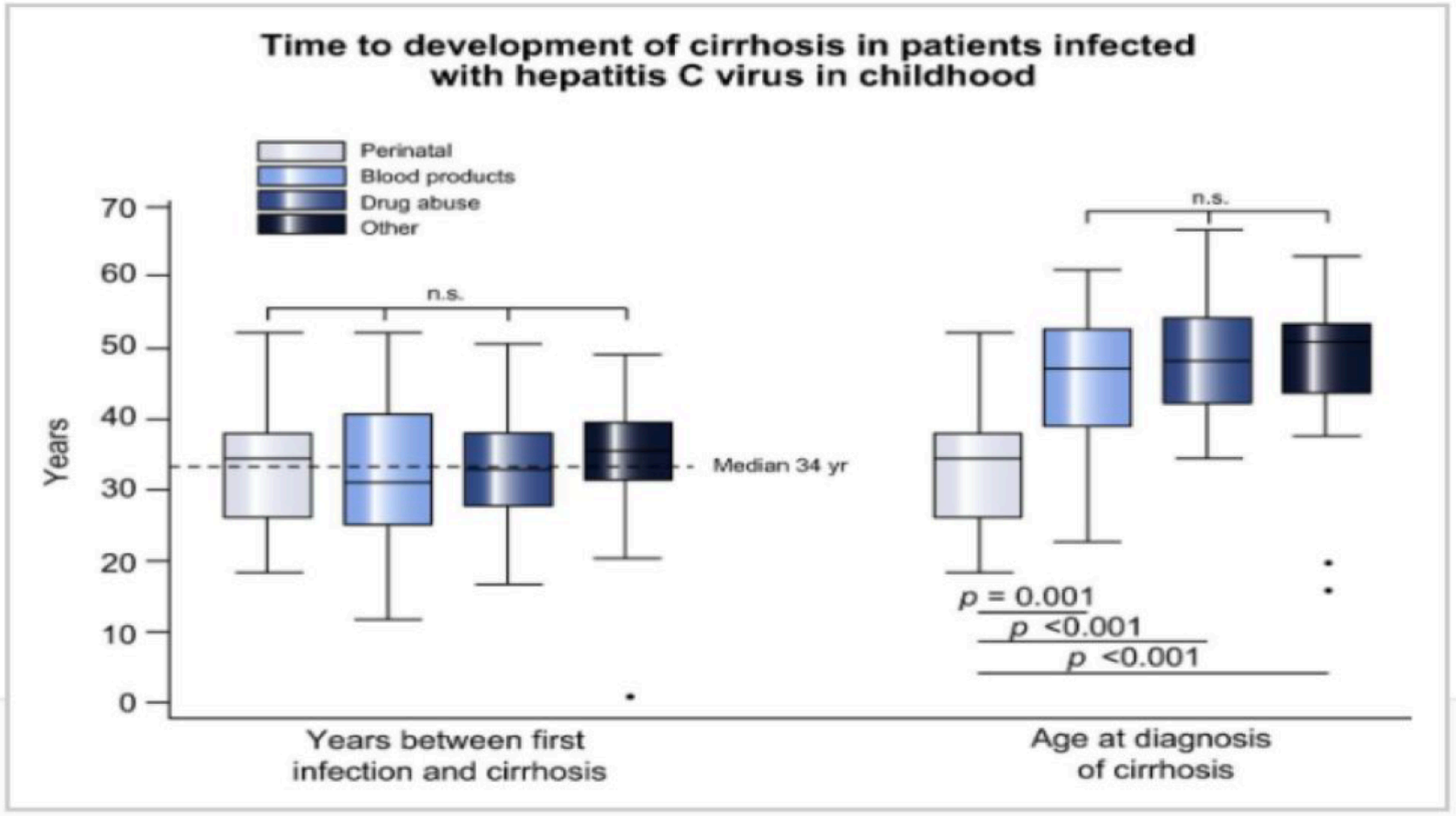
Hepatitis C in Children

Natural history of the infection



Modin J, J Hepatol 2018

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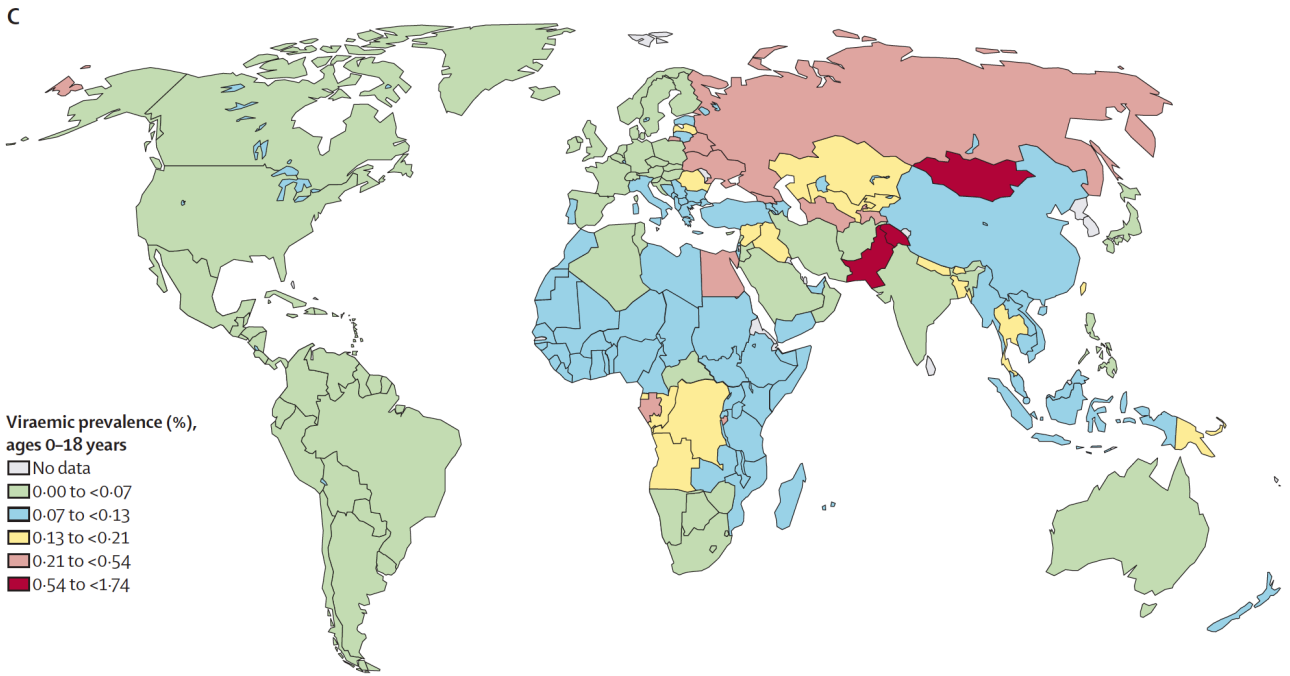
Global Burden of HCV in Children and Adolescents in 2018

- 3.26 (2.07-3.9) million viraemic children (1 - 18 years of age) worldwide (0.13%; 95% UI 0·08–0·16)



Schmelzer J, Lancet Gastroenterol Hepatol 2020

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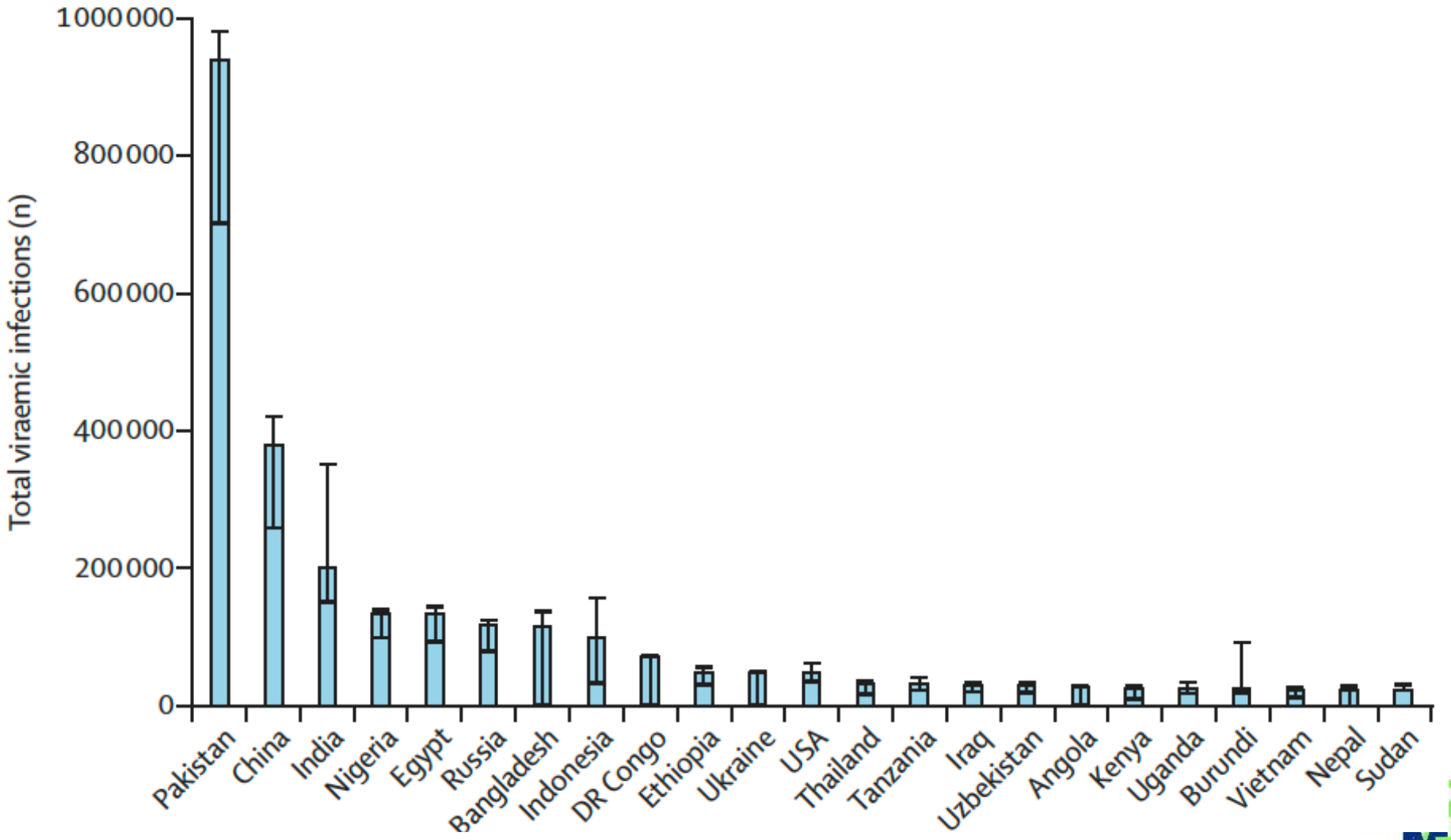
Global Burden of HCV in Children and Adolescents in 2018



Schmelzer J, Lancet Gastroenterol Hepatol 2020

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Protocol Synopsis

Study Title	A Phase 2/3, Open-Label, Multicentre, Single arm, multi-cohort trial to Investigate the Pharmacokinetics, Safety, Acceptability and Efficacy of the of Sofosbuvir (SOF) in combination with Daclatasvir (DCV) in treatment-naïve, non-cirrhotic adolescents and children with Chronic HCV Infection
Sponsor	PENTA Foundation
Principal Investigator and pharmacologist	Giuseppe Indolfi Tim Cressey (Pharmacology)
Study Centers Planned	Involvement of study sites in several HCV prevalence countries is being considered: Egypt, Ukraine (with UNICEF), Mongolia, Uzbekistan, India-Punjab, Pakistan (PENTA training scheduled early 2020) and Georgia
Rationale	To achieve WHO's goals by 2030, it is pivotal to understand the current challenges associated with HCV elimination worldwide and undertake strategic efforts to overcome these challenges. In the absence of a vaccine, HCV treatment is central to infection control. In recent years, the new DAA combinations have revolutionized the treatment of chronic HCV infection globally. These treatments have excellent efficacy and safety both in adults and children with over 90% rates SVR. The few side effects, the short treatment durations (as short as 8 weeks) have dramatically improved patient adherence relative to the previous standard of care – pegylated interferon and ribavirin. Although an increasing number of DAAs have gained approval for adults since 2011 worldwide, the expansion of DAA treatment to adolescents and children and access to DAA for these populations remains slow and limited. DAA regimens are still largely unaffordable to many children and adolescents worldwide. In the context of the Global Accelerator for Paediatric Formulations (GAP-f) led by the World Health Organization, the development of a child appropriate combination of sofosbuvir and daclatasvir has been prioritized to cover the needs of children older than 3 years of age.

Dual Sofosbuvir/Daclatasvir Therapy in Adolescent Patients With Chronic Hepatitis C Infection

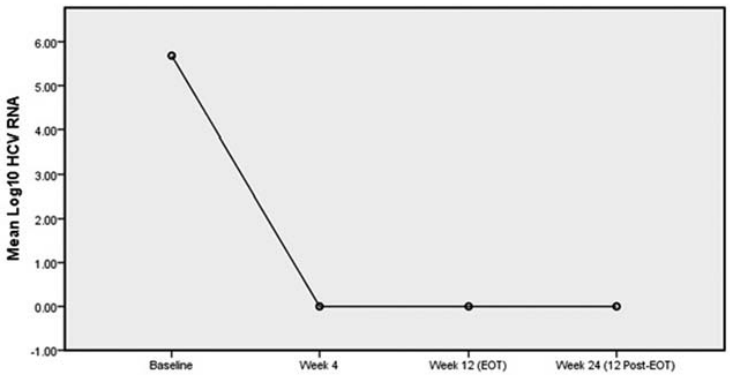
*Mostafa Yakoot, †Mortada H. El-Shabrawi, ‡Manal M. AbdElgawad, ‡Aml A. Mahfouz, §Sherine Helmy, ||Alaa M. Abdo, and ¶Hisham R. El-Khayat

- Test safety and efficacy of SOF/DCV in patients **12 to 17 years old** with chronic HCV, genotype 4 infection
  - 30 chronic HCV-infected adolescents

- Daily dose of SOF/DAC based on body weight categories: ~400 mg/1.7m^2 or 60 mg/1.7m^2
  - **20-30 kg**: SOF 200mg / DAC 30 mg
  - **>30-40 kg**: SOF 300mg / DAC 45 mg
  - **>40 kg**: SOF 400mg / DAC 60mg

- SVR12 rate was 29 of 30 (96.7%; 95% [CI] 83.3%–99.4%)
  - one child lost to follow-up after viral negativity at end of Rx

Virologic response kinetics curve



Yakoot et al JPGN Volume 67, Number 1, July 2018.

ORIGINAL ARTICLE

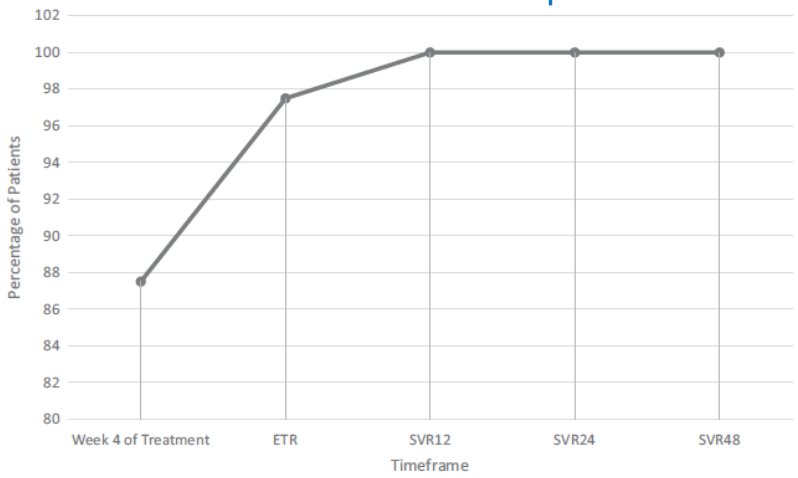
WILEY JOURNAL OF VIRAL HEPATITIS JVH

Safety and efficacy of combined sofosbuvir/daclatasvir treatment of children and adolescents with chronic hepatitis C Genotype 4

- Investigate the safety and efficacy of SOF/DCV for HCV Genotype 4 in **children aged 8 to 18 yrs or >17 kg**
- 40 chronic HCV-infected, treatment-naïve children with well compensated livers (45% <12 years)
  - **>45 kg**: SOF 400 mg/d, DAC 60 mg/d for 12 weeks
  - **17 to 45 kg**: SOF 200 mg/d, DAC 30 mg/d for 12 weeks

- SVR12 and SVR24 were 97.5% and 95%, respectively
- Observed side effects:
  - Mild and none required drug cessation

Viral clearance of patients



Abdel Ghaffar et al J Viral Hepat. 2019;26:263–270.

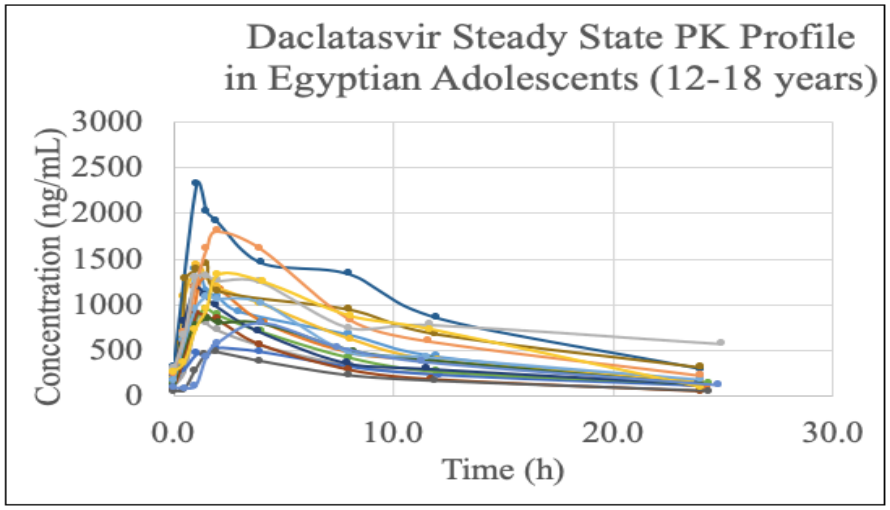
New DAC PK Data: SOF/DAC in Adolescents

- Clinical trial of Daclatasvir in Egyptian Adolescents: SOF/DAC: 400/60 mg/daily

PK Parameters for Daclatasvir in Egyptian Adolescent HCV genotype 4 Infected Patients

Steady State PK Parameters for Daclatasvir in Egyptian Adolescent HCV genotype 4 Patients*	
Parameter	mean±standard deviation
t1/2 (h)	9.03 ±3.26
Tmax (h) (median, range)	1.5 (1-2)
Cmax (ng/mL)	1175.15±456.18
AUC 0-24 (ng*h/mL)	12231.27±5314.25
AUC 0-inf (ng*h/mL)	14886.52±7819.96
V/F_obs (mL)	1040.35±499.02
Cl/F_obs (mL/min)	83.98±40.88

Dose: daclatasvir 60 mg and sofosbuvir 400mg once daily orally for 12 weeks



El-Sayed et al, under publication
Courtesy of M. Abbassy, S. Farid

Al Nahaari MM et al Antiviral Therapy 2020

Question

What is the optimal dose for DAC in children below 12 years of age in the context of a public health approach?

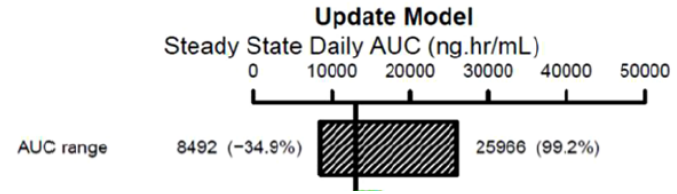
- What age (body weight) can we safety use the adult dose of DAC/(SOF)?
- Use of the adult generic fixed dose combination (SOF/DAC, 400/60mg) in young children?
- Other options:
  - Half-tab of Adult FDC (currently non-scored)?
  - Score - adult FDC tablet?
  - use 30 mg DAC + 200 mg SOF (no genetic available)

Current Objectives: DAC Simulations

- To estimate daclatasvir drug exposures in children with body weights 17 to 35 kg receiving 60 mg DAC, once daily

- To estimate daclatasvir drug exposures in children with body weights 17 to 35 kg receiving 30 mg DAC, once daily

Simulations: DAC AUC



DAC 30 vs 60 mg over the 17 - <35 kg weight band

Based on daily AUC

DAC 30 mg, twice daily

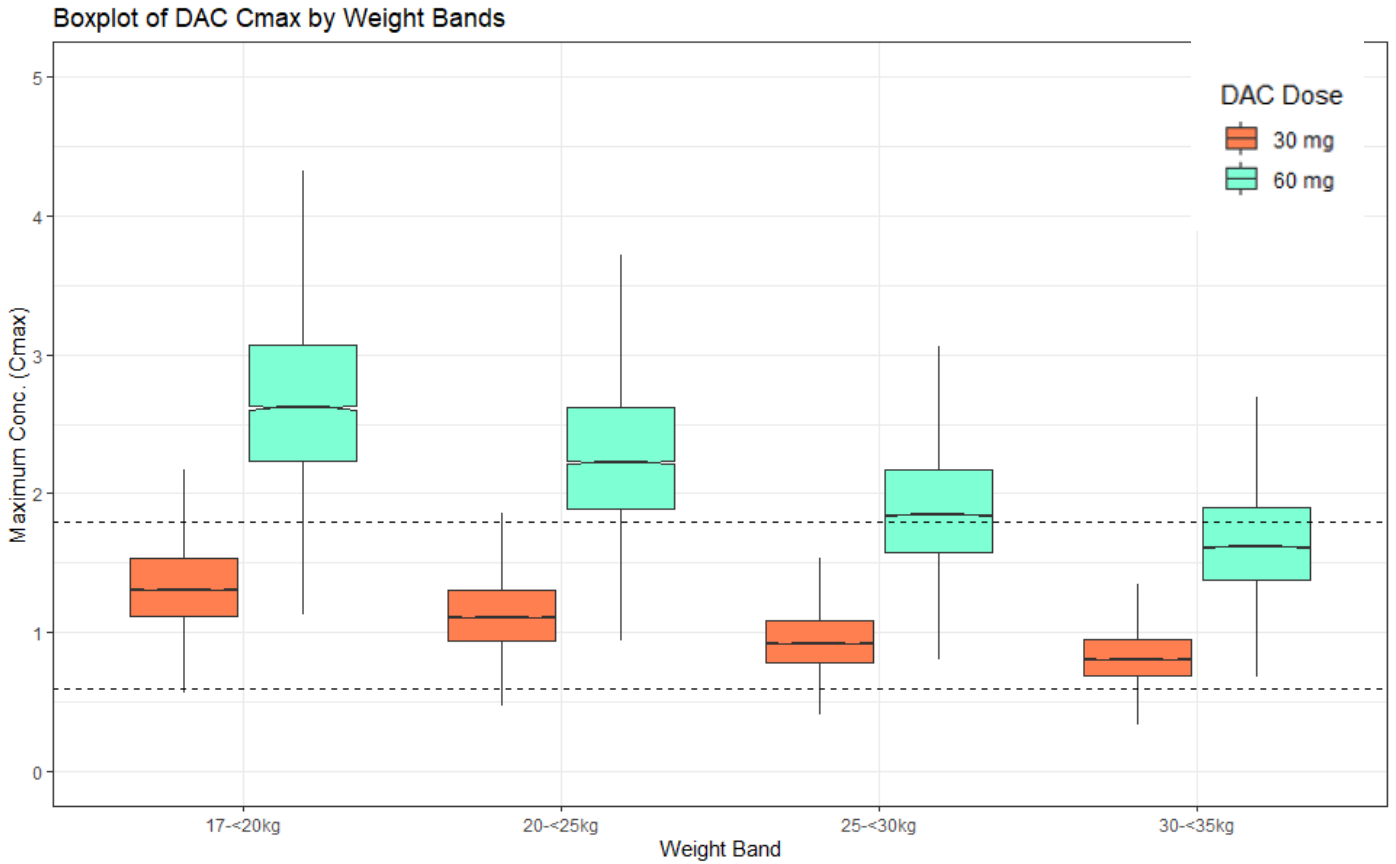
*Adult DAC exposure
5th to 95th percentile
(6.15 to **25.96** µg.hr/mL)

Osawa et al 2019 Clin. Pharm DD; 8(6) 802–817

*Chan et al 2017 Clin. Pharm; 56; 1173-1183

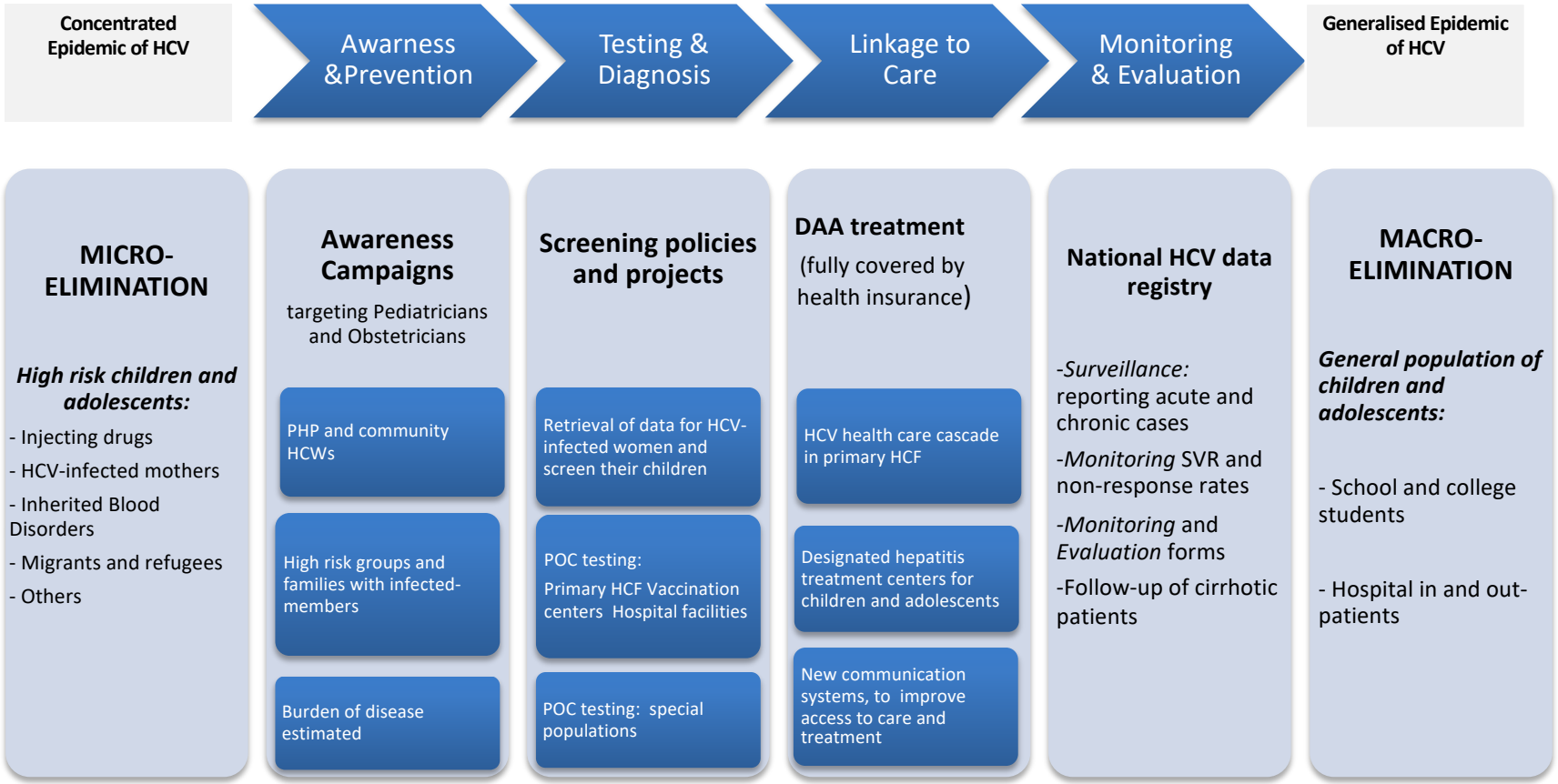
Simulations: DAC Cmax

DAC 30 vs 60 mg over the 17 - <35 kg weight band



*Adult DAC Cmax
5th to 95th percentile
(0.568 to 1.804 µg.hr/mL)

*Chan et al 2017 Clin. Pharm; 56; 1173-1183

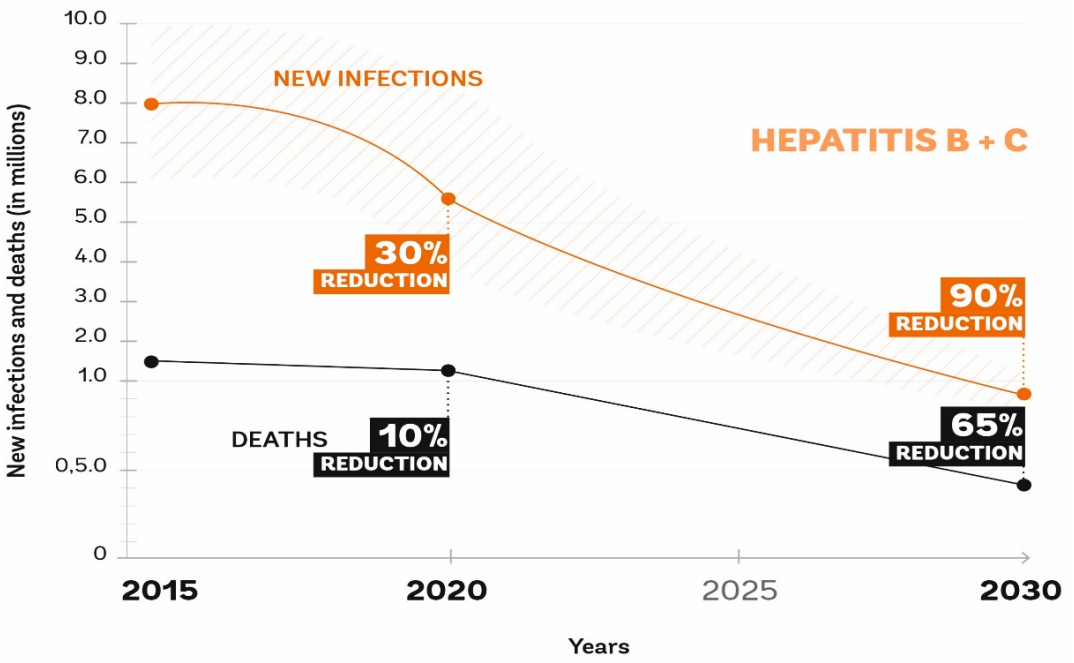


PHP, primary health care physicians; HCWs, health care workers; POC, point of care; HCF, health care facilities; DAA, direct-acting antivirals; SVR, sustained virological response.

El-Sayed & Indolfi, Seminars Liver Dis 2020

Global Viral Hepatitis Strategy – a roadmap to Elimination

Eliminate viral hepatitis as a major public health threat by 2030, as defined by:



	Interventions	Indicator	2015 baseline	Targets 2020	Targets 2030
1	Hepatitis B vaccination	HEPB3 coverage	84%	90%	90%
2	HBV PMTCT[a]	HEP vaccine birth dose coverage	39%	50%	90%
3	Blood safety	Donations screened with quality assurance	97%	95%	100%
	Injection safety	Proportion of unsafe injections	5%	0%	0%
4	Harm reduction	Syringes & needles distributed/PWID/year	27	200	300
5	Testing services	% HBV-infected diagnosed	9%	30%	90%
		% HCV-infected diagnosed	20%	30%	90%
	Treatment	% diagnosed with HBV on treatment	8%[b]	–[c]	80%[d]
		% diagnosed with HCV started on treatment	7%[b]	–[c]	80%[d]

Courtesy of Philippa Easterbrook, WHO