DOT of Sofosbuvir/Ribavirin +/- Peginterferon with Minimal Monitoring for the Treatment of Hepatitis C in PWUD in Chennai, India (C-DOT)

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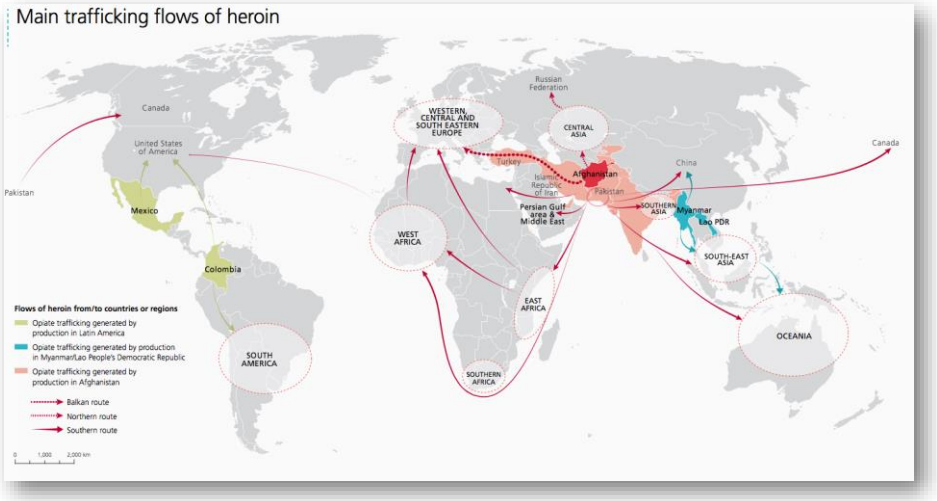
HCV in India

- Estimated 6.3 million HCV viremic persons
- Primary modes of transmission:
  - Contaminated medical injections
  - Blood and blood products
  - Injection drug use

Injection Drug Use & India



Source:World Drug Report 2016

HCV in India

- Estimated 6.3 million HCV viremic persons
- Primary modes of transmission:
  - Contaminated medical injections
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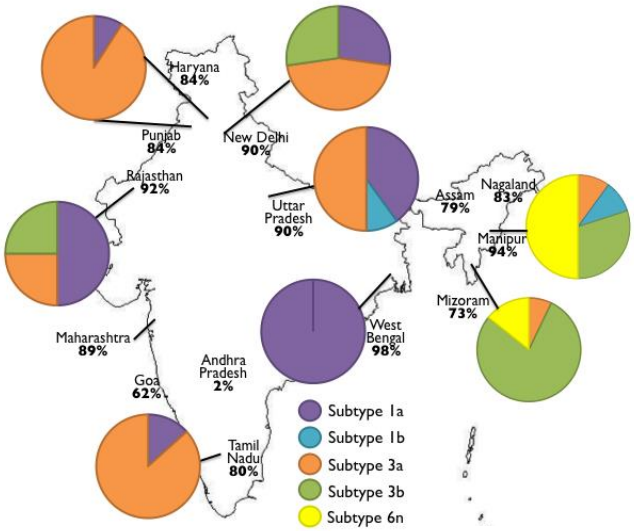
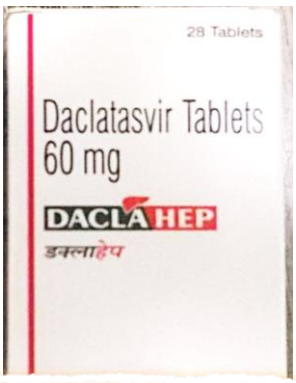
- Distribution of HCV genotypes

HCV Genotypes in India



Source: Solomon SS, CROI 2013

HCV in India



Generic SOF ushers in a new era for HCV treatment!

HCV in India

- Estimated 6.3 million HCV viremic persons
- Primary modes of transmission:
  - Contaminated medical injections
  - Blood and blood products
  - Injection drug use
- Distribution of HCV genotypes
- Optimal strategy to deliver HCV therapy to PWID unclear
- DOT is the cornerstone of TB treatment in India

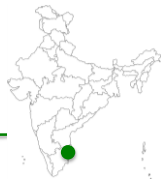
Hypothesis

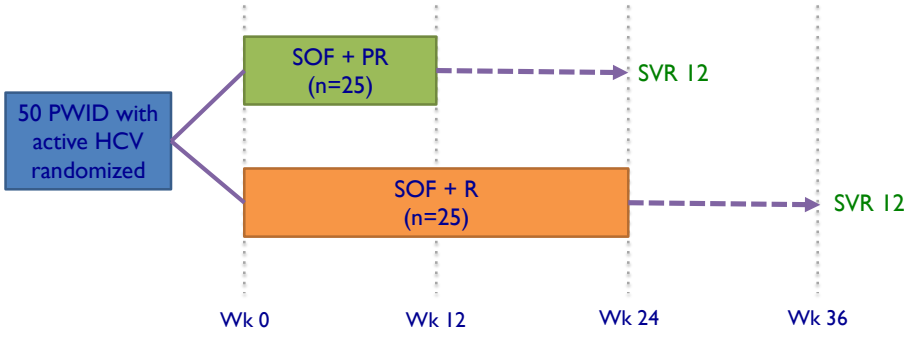
"Directly observed therapy will be associated with high rates of treatment completion and SVR among people who use drugs in Chennai, India"

Eligibility Criteria

- Inclusion Criteria:
  1. ≥18 years of age
  2. Written informed consent
  3. History of drug use or active drug use
  4. HCV RNA+
  5. HCV treatment naïve
  6. ALT ≤10 ULN
  7. AST ≤10 ULN
  8. Hgb>12 (males) and >11 (females)
- Exclusion criteria:
  1. Active HBV infection (HBsAg positive)
  2. Evidence of decompensated cirrhosis
  3. Pregnant OR partner pregnant

Methods





- Stratified blocked randomization with varying block sizes was used

Methods

- Study started September 2015
- SOF+PR and SOF+R only two generic pangenotypic regimens available at the time
  - SOF (Spegra, Emcure Pharmaceuticals Ltd)
  - RBV (Univirin, Unison Pharmaceuticals)
  - PEG alfa 2a (Taspiance, Emcure Pharmaceuticals Ltd)

Generic SOF, PEG and RBV

Methods

- Study started September 2015
- SOF+PR and SOF+R only two generic pangenotypic regimens available at the time
- Medication delivery by DOT
  - Weekly clinic visit for PEG injections in SOF+PR arm (INR 100 compensation)
  - SOF+RBV delivered in the field by outreach workers after confirmation of identity (biometric)

Laboratory testing/monitoring

	Week							
	0	4	8	12	16	20	24	36
HCV RNA	X						X*	X**
HCV genotyping								
CBC	X	X	X	X	X**	X**	X*,**	
LFT				X*,**			X*,**	X**
***only in the SOF+PR arm; ** only in the SOF+RBV arm**								

Statistical Methods

- Primary analyses were Intention to Treat (ITT), missing=failure
- Fishers exact test and Mann Whitney U test were used to compare categorical and continuous variables, respectively
- As treated (AT) analyses conducted among those who completed treatment (n=44) to identify factors associated with SVR

Demographic and clinical characteristics

	SOF+PR (n=25)	SOF+RBV (n=25)
Median age in years, (IQR)	46 (41 – 50)	46 (44 – 47)
Male, n(%)	25 (100)	25 (100)
Median monthly income, in USD (IQR)	90 (68 – 1290)	90 (72 – 150)
History of substance use in the prior month, n(%)	13 (52)	12 (48)
Liver stiffness category, n(%)		
• *<8 kPa*	15 (60)	12 (48)
• *8-12.3 kPa*	5 (20)	8 (32)
• *>12.3 kPa*	5 (20)	5 (20)
FIB-4 Index, n(%)		
• *Class 1, ≤1.45*	6 (24)	7 (28)
• *Class 2, 1.46 - 3.25*	16 (64)	11 (44)
• *Class 3, >3.25*	3 (12)	7 (28)
Median HCV RNA in $\log_{10}$ copies/ml, (IQR)	6.5 (6.1 – 6.6)	6.1 (5.5 – 6.7)
HCV Genotype, n(%)		
• *1a*	2 (8)	5 (20)
• *3a*	22 (88)	20 (80)
• *6n*	1 (4)	0
HIV co-infected, n(%)	0	2 (8)
Median HOMA-IR	1.3 (0.7 – 3.4)	2.4 (1.1 – 5.6)

Primary and Secondary Outcomes

	Arm 1 (N=25) 12 weeks SOF+PR	Arm 2 (N=25) 24 weeks SOF+R	p-value
Primary outcome			
Treatment completion, n(%)	22 (88.0)	22 (88.0)	>0.99
Secondary outcomes			
Sustained virologic response*, n(%)	22 (88.0)	15 (60.0)	0.05
Median number of serious adverse events, IQR	0	0	
Median change in insulin resistance (HOMA-IR), IQR	1.2 (-0.1, 9.1)	0.1 (-1.3, 6.1)	0.30
Other outcomes			
Percentage completed doses			
• *0–30%*	3 (12)	3 (12)	
• *75–90%*	3 (12)	2 (8)	0.93
• *>90–95%*	2 (8)	4 (16)	
• *>95%*	17 (68)	16 (64)	

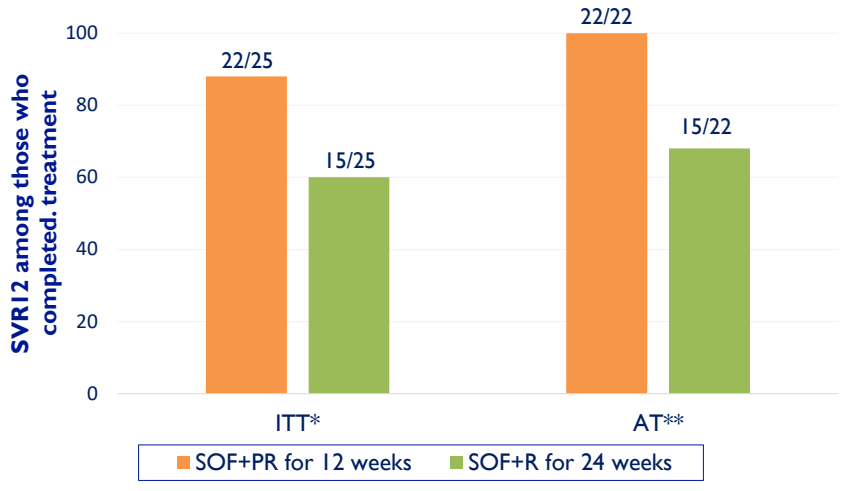
Real-world challenges

Real-world challenges

Rx discontinuation and failures

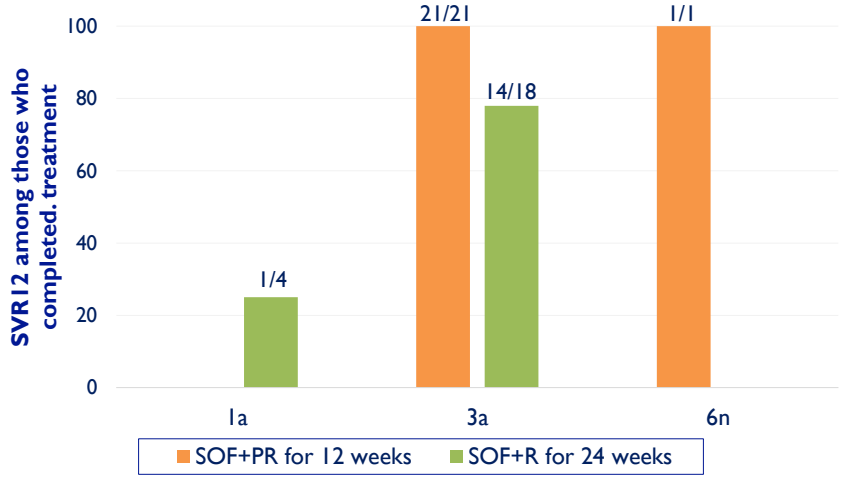
- Rx Discontinuation (n=6):
  - 3/6 discontinued in Week 1
  - 3/6 discontinued beyond Week 4
  - 2/6 reported substance use in prior month
- Rx failures (SOF+R; n=7)
  - All reported substance use in the prior month
  - 5/7 had HCV RNA ≤LLOQ at EOT
  - 4 were GT3 and 3 were GT1

Sustained virologic response

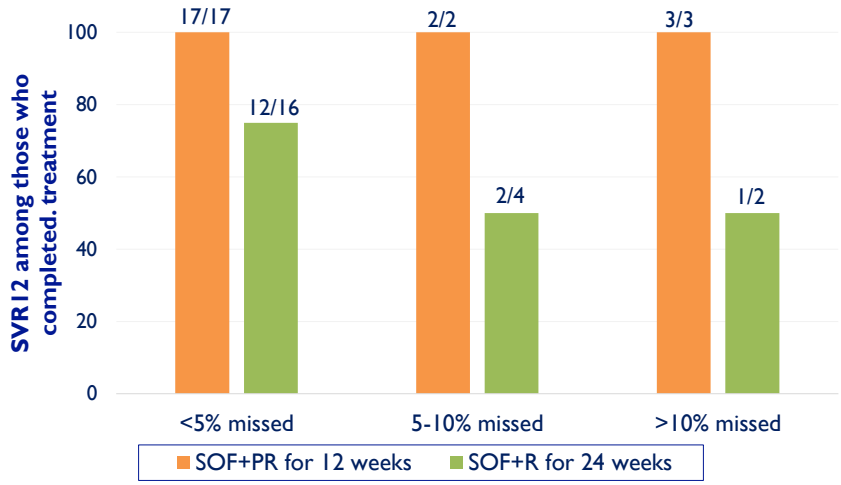


*p=0.05; **p<0.01

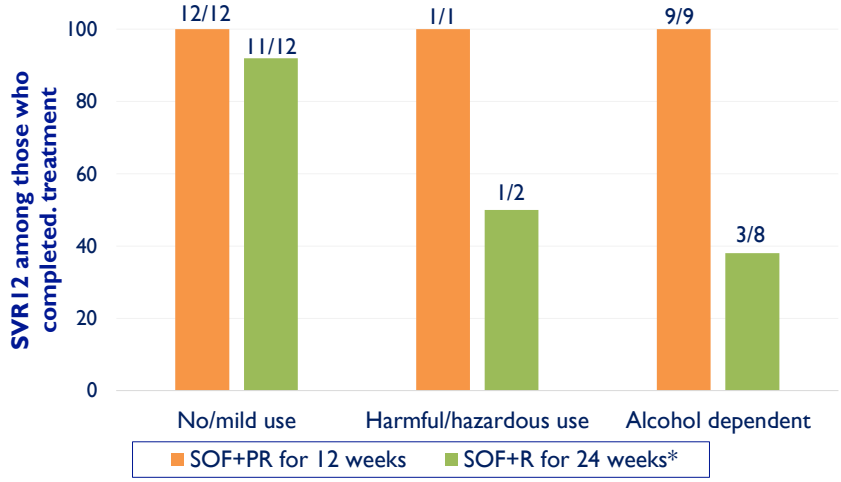
SVR by genotype (AT)



SVR by missed doses (AT)

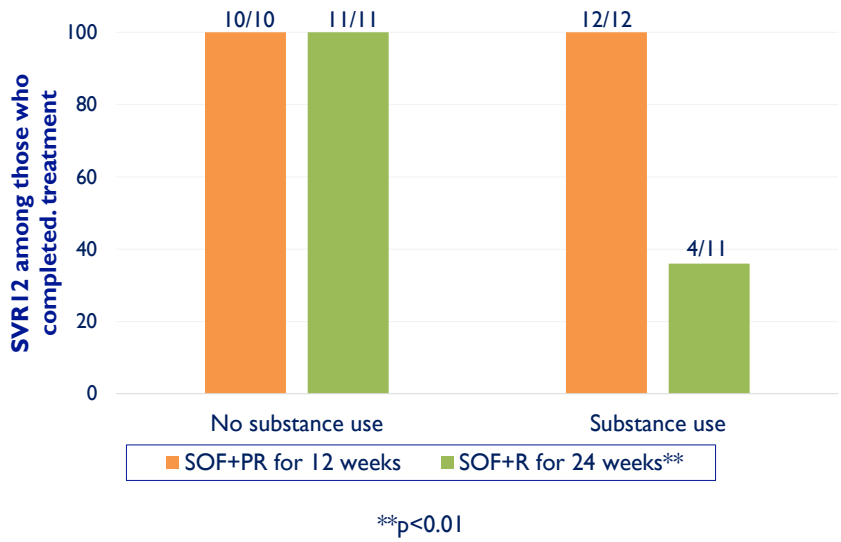


SVR by AUDIT (AT)



*p=0.03

SVR by substance use (AT)



**p<0.01

Conclusions

- Field-based DOT with minimal molecular monitoring was feasible for the delivery of HCV therapy to current and former substance using populations in India
  - 100% adherence was still challenging
- SOF+PR was superior to SOF+R particularly among those with ongoing substance use
- Role of PEG in shortening therapy worthy of further investigation particularly in settings where injections are viewed favorably

Acknowledgements

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