Aderenza alla terapia e effetti collaterali

Cosimo Colletta
Medicina Interna
Epatologia COQ
ASL VCO

Adherence to antiviral therapy

- Is critical to achieving a SVR
- Persistence with antiviral regimens can pose challenges for patients

1. Missing doses and dose-timing errors
2. Facilitators of adherence
3. Barriers to adherence

Treatment adherence facilitation

- The "80/80/(80) rule" defines optimal adherence as having taken at least 80% of prescribed doses at least 80% of the time

- It is unclear what level of adherence is optimal to achieve SVR with non-interferon-based regimens

Drug levels, Genetic barrier and the virus

	HIV	HBV	HCV
Virus			
daily production of virions per day	10^{10}	10^{12}–10^{13}	10^{12}
half-life of free virions (h)	1	3–24	2–3
half-life of intracellular virions	days (dependent on infected cells $t_{1/2}$)	months (dependent on infected cells $t_{1/2}$)	hours (not dependent on infected cells $t_{1/2}$)
mutation rate	very high	high	very high
constraints due to ORFs in targeted viral enzymes	moderate	high	none
immune-mediated escape mutants	frequent	infrequent	frequent
Target cells			
half-life of infected cells	days	months	weeks
size of susceptible cells compartment	large	small	probably large
intracellular viral reservoir	yes (integr	yes (cccDNA)	no

Hangfei Qi et al. Current Opinion in Virology 2015, 14:62–70

DAA treatment adherence

- Furthermore, it is not yet known whether adherence to DAAs is problematic enough to warrant targeted intervention

- In clinical trials to date, DAA treatment adherence and completion rates have been extremely high, but it remains to be seen how this will play out in real-world clinical practice

Facilitators of adherence

- Few dose-timing deviations, but several more occurrences of delays in dosing
- Facilitators of adherence fell into 2 broad categories:

(a) patient knowledge and motivation

(b) practical behavioral strategies and routines

Barriers to adherence

- Barriers to adherence involved changes in daily routine, being preoccupied with family or work responsibilities, and sleeping through dosing times

- A few patients reported skipping doses due to side effects

Barriers to adherence

- Patients with previous hepatitis C virus treatment experience may have fewer dose-timing errors
- A high level of anxiety among some patients was discovered regarding dosing errors
- Emotional and informational support from clinical and research staff was key to assuaging patient fears

Communication SE

- Confidence to communicate with health care provider
- Confidence to cope with physical side effects
- Confidence to cope with psychiatric side effects
- Confidence to take all medications as prescribed and attend doctor visits

Analysis of patient interviews

1. Motivations for commencing CHC treatment
2. Information and feedback should be personalised to the needs and lifestyles of patients
3. Facilitators of treatment adherence: social, emotional and practical support
4. Barriers to treatment adherence include side effects, stigma, a complicated dosing schedule and limitations of the public healthcare system

Sian K. Smith et al. Psychology & Health Volume 30, Issue 8, 2015

Treatment-related factors

Several treatment-related factors may lead patients to terminate therapy early

- Longer treatment durations
- Higher complexity regimens
- Frequent or intolerable AEs

Effect of HIV co-infection on adherence to a 12-week regimen of hepatitis C virus therapy with ledipasvir and sofosbuvir

AIDS: Post Acceptance: October 30, 2015

Adherence to LDV/SOF in this urban population was high and comparable between HCV monoinfected and HIV/HCV coinfected participants regardless of antiretroviral use

Townsend, Kerry; Petersen, Tess; Gordon, Lori A; Kohli, Anita; Nelson, Amy; Seamon, Cassie; Gross, Chloe; Tang, Lydia; Osinusi, Anu; Polis, Michael A.; Masur, Henry; Kottilil, Shyam

Currently DAA treatment regimens

- SOF and LDV are well tolerated with very few treatment discontinuations (1%)
- The most common side effects included headache, fatigue, nausea, insomnia and diarrhea
- Adverse effects were more common in the treatment arms that included RBV
- SVR rates were very high in RBV-free arms, and any additional benefit gained by adding RBV

Simeprevir with sofosbuvir

- The most common side effects are fatigue, headache and nausea
- Anemia and increased levels of bilirubin are observed in the regimens containing RBV
- Discontinuation was seen only in the 24-week arms at a low rate of 2%
- Serious adverse events (4–8%) and adverse events leading to treatment discontinuation (1.4%) were relatively low

Scott J et al. BMC Infect Dis. 2014 Aug 26;14:465.

Paritaprevir/r+Ombitasvir + Dasabuvir

- Common reported side effects: headache, fatigue and nausea. The rate of discontinuation was very low, ranging from 0 to 2%
- Elevations of ALT > 5N were noted in 1% of subjects
- These elevations were asymptomatic and typically resolved within the first 2 months of treatment
- Elevation of ALT occurred more frequently in patients using ethinylestradiol
- Elevation of bilirubin > 2N, was also noted in 2% of subjects in the RBV-free arms.

Adverse Events

	SOF+LDV (12 ws)	SOF+SIM (12 ws)	PTV/r+OBV+DSV (12 ws)
FATIGUE	13%	38%	29%
HEADACHE	14%	23%	26%
NAUSEA	7%	17%	9%
DIARRHEA	3%	17%	11%
INSOMNIA	5%	18%	6%

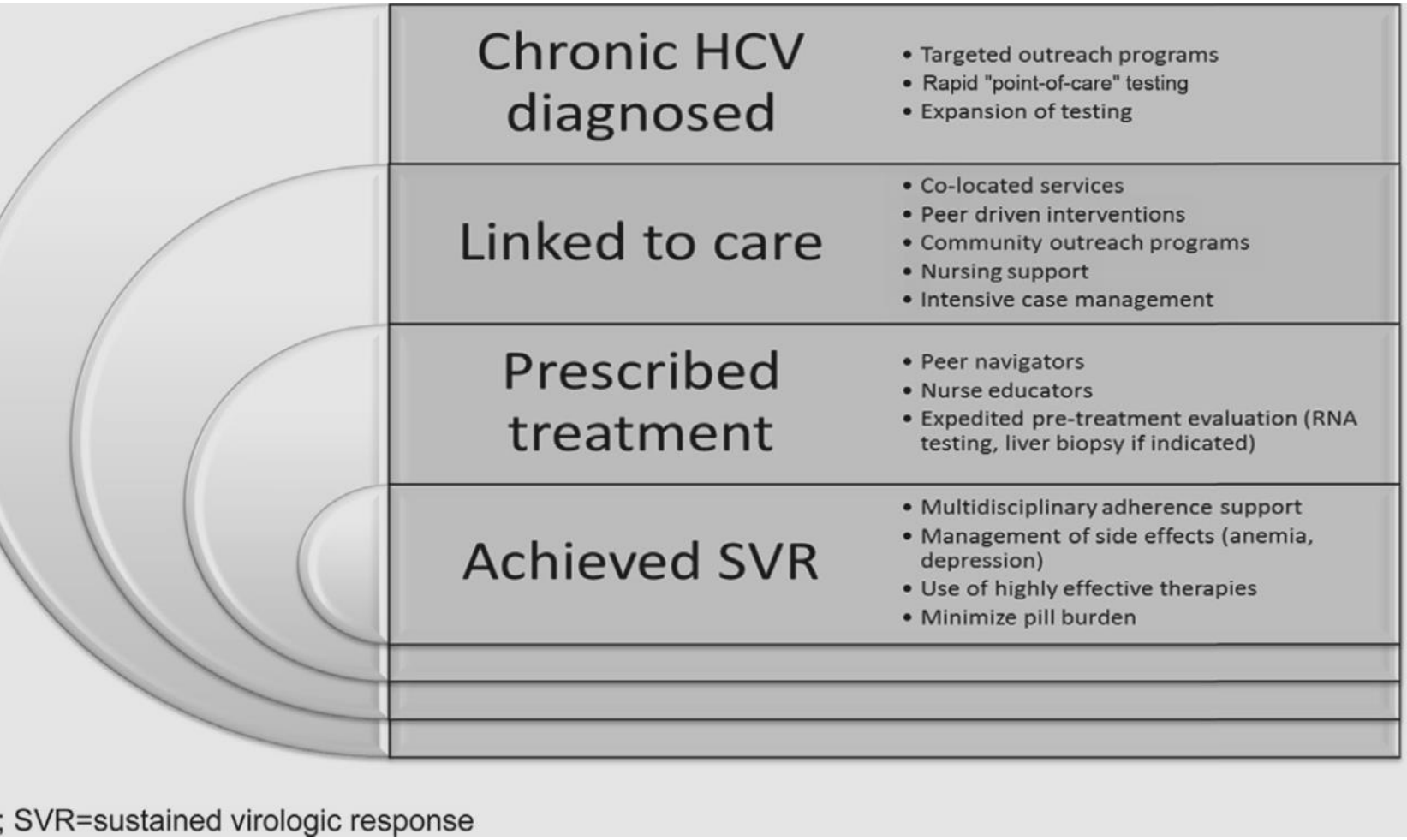
Adverse Events during the Treatment Period

Adverse Event	Previously Untreated					Previously Treated	
	Treatment for 24 Wk			Treatment for 12 Wk		Treatment for 24 Wk	
	Groups A and B: Lead-in SOF and DCV (N=31)	*Groups C and D: DCV and SOF (N=28)*	*Groups E and F: DCV and SOF and RBV (N=29)*	*Group G: DCV and SOF (N=41)*	*Group H: DCV and SOF and RBV (N=41)*	*Group I: DCV and SOF (N=21)*	*Group J: DCV and SOF and RBV (N=20)*
	number of study participants (percent)						
Any adverse event	25 (81)	26 (93)	26 (90)	38 (93)	38 (93)	16 (76)	20 (100)
Adverse event occurring in ≥25% of patients in any group*							
Fatigue	9 (29)	14 (50)	9 (31)	16 (39)	15 (37)	6 (29)	9 (45)
Headache	5 (16)	8 (29)	11 (38)	14 (34)	9 (22)	7 (33)	7 (35)
Nausea	5 (16)	9 (32)	9 (31)	8 (20)	8 (20)	0	2 (10)
Grade 3 or 4 adverse event	0	2 (7)†	2 (7)	1 (2)	1 (2)	0	1 (5)
Discontinuation of treatment due to adverse event‡	0	1 (4)	1 (3)	0	0	0	0
Serious adverse event§	2 (6)	4 (14)	2 (7)	1 (2)	0	0	1 (5)
Grade 3 or 4 laboratory abnormality occurring in ≥3 patients across all groups							
Phosphorus <2.0 mg/dl	0	1 (4)	1 (3)	0	3 (7)	0	0
Glucose							
Fasting value >250 mg/dl	0	1 (4)	1 (3)	1 (2)	0	1 (5)	0
Random value >250 mg/dl	0	0	1 (5)¶	0	0	1 (5)	1 (5)

Parameter, n (%)[a]	All patients N = 152
Death	0
Serious adverse events	1 (1)[b]
Adverse events leading to discontinuation	0
Grade 3 adverse events	3 (2)[c]
Grade 4 adverse events	0
Adverse events in ≥ 10% of patients (all grades)	
Headache	30 (20)
Fatigue	29 (19)
Nausea	18 (12)
Treatment-emergent grade 3/4 laboratory abnormalities	
Hemoglobin < 9.0 g/dL	0
Absolute neutrophils < 0.75×10^9 /L	0
Absolute lymphocytes < 0.5×10^9 /L	1 (1)
Platelets < 50×10^9 /L	2 (1)
International normalized ratio > 2 × ULN	2 (1)
Lipase > 3 × ULN	3 (2)

Adverse Events

	PTV/r+OBV NAIVE	PTV/r+OBV+RBV NAIVE	PTV/r+OBV+RBV EXPERIENCED
DRUG DISCONTINUATION	0%	0%	0%
FATIGUE	7%	12%	18%
HEADACHE	30%	33%	29%
NAUSEA	9%	17%	12%
DIARRHEA	5%	14%	6%
INSOMNIA	5%	10%	16%
ASTHENIA	25%	24%	33%
MYALGIA	0%	0%	10%
NASOPHARYNGITIS	5%	5%	12%
PRURITUS	5%	2%	10%



; SVR=sustained virologic response

An adherence monitoring program

- The program should involve clinical pharmacists, nurse care managers, dispensing pharmacists, and prescribers

- The selection of a regimen with the best chance of virologic cure, along with provision of medication adherence monitoring and overall therapy management, is critical to treatment success.

Bonner JE et al. J Clin Gastroenterol. 2015 Jan;49(1):76-83

The telephonic prescriber program

- To promote use of a cost-effective regimen through telephonic prescriber outreach on prior authorization requests
- Monitor patient adherence to treatment using pharmacy claims data
- Identify patients achieving virologic cure by conducting prescriber outreach

Management of HCV infection

- The appropriate management of HCV infection is complex and depends heavily on:
- Clear communication
- Collaboration between patients and members of the healthcare team to minimize

✓ Adverse treatment effects

✓ prevent drug-drug interactions

✓ ensure treatment adherence

Conclusion

- To increase treatment adherence and completion rates, a patient-centred approach is required that addresses patients' social, practical, and emotional support needs and adaptive coping strategies.
- However, patients often have difficulty adhering to HCV treatment because of factors such as the psychiatric side effects of regimens and social disadvantage

Conclusion

- ✓ When comprehensive shared-care was limited or unavailable, physicians and nurses filled in the gaps by assuming roles outside of their expertise to help patients adhere to HCV treatment.
- ✓ Physicians and nurses applied instrumental support strategies based on psychosocial interventions, namely patient advocacy, pragmatic problem-solving, treatment engagement and emotional support.