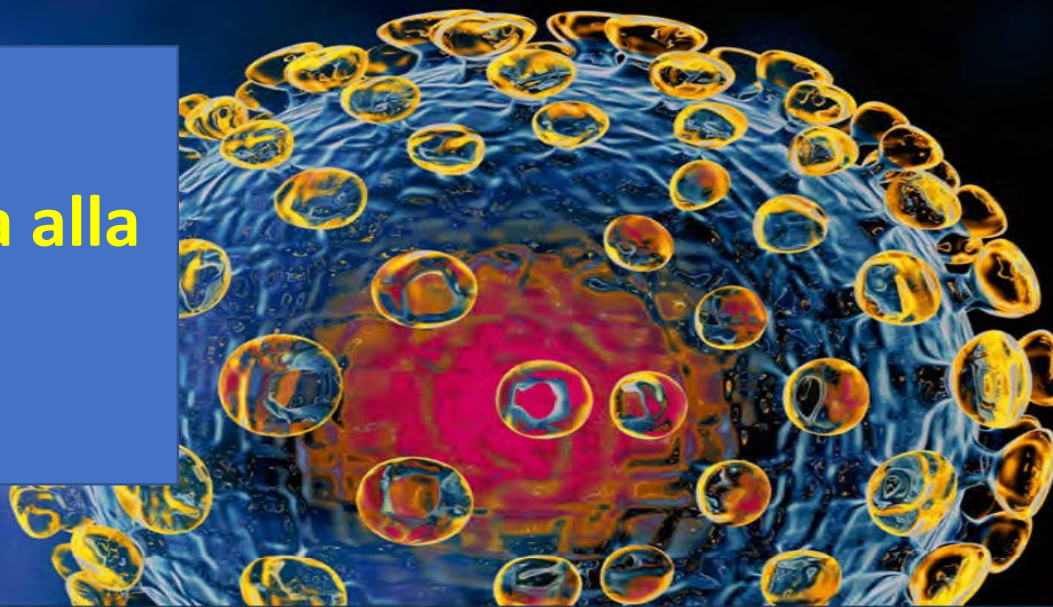


EPATITE C : Dalla scoperta alla eliminazione



Alfredo Alberti

Senior Professor

Università di Padova

Ricercatore Emerito

Istituto Veneto di Medicina Molecolare



OUTLINE DI QUESTA PRESENTAZIONE

- EPATITE C : i primi 40 anni pre-DAA
- La rivoluzione dei DAA
- I risultati già acquisiti con DAA
- La prospettiva di eliminazione di HCV

1975 :

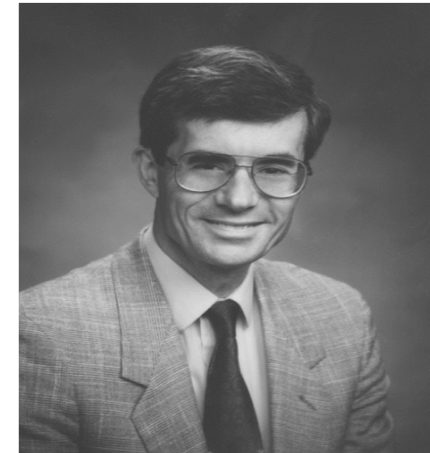
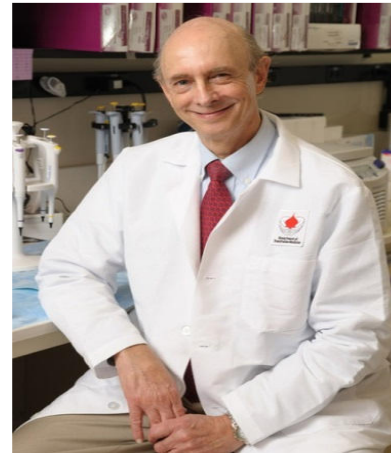
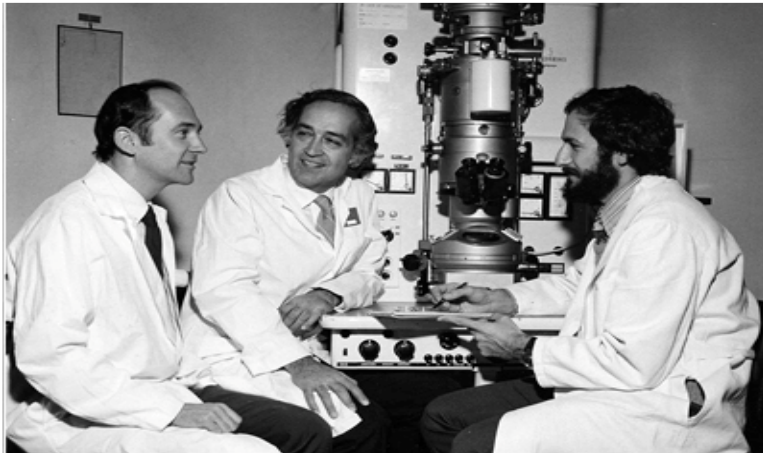
LA DESCRIZIONE DELLA EPATITE NANB

April 10, 1975

THE NEW ENGLAND JOURNAL OF MEDICINE

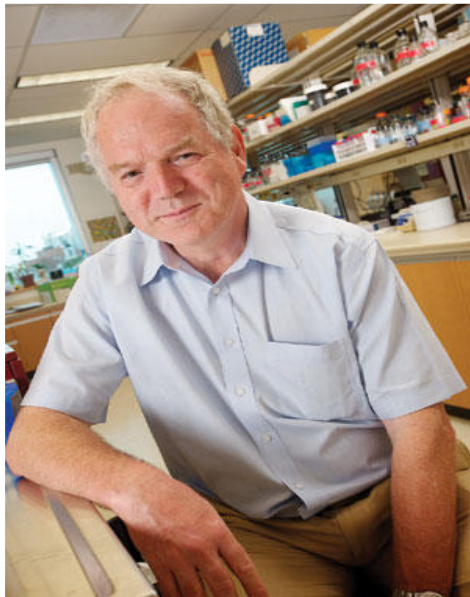
TRANSFUSION-ASSOCIATED HEPATITIS NOT DUE TO VIRAL HEPATITIS TYPE A OR B

STEPHEN M. FEINSTONE, M.D., ALBERT Z. KAPIKIAN, M.D., ROBERT H. PURCELL, M.D.,
HARVEY J. ALTER, M.D., AND PAUL V. HOLLAND, M.D.



1989

LA SCOPERTA DI HCV



SCIENCE, VOL. 244

21 APRIL 1989

Isolation of a cDNA Clone Derived from a Blood-Borne Non-A, Non-B Viral Hepatitis Genome

QUI-LIM CHOO, GEORGE KUO, AMY J. WEINER, LACY R. OVERBY,
DANIEL W. BRADLEY, MICHAEL HOUGHTON

21 APRIL 1989

SCIENCE, VOL. 244

An Assay for Circulating Antibodies to a Major Etiologic Virus of Human Non-A, Non-B Hepatitis

G. KUO, Q.-L. CHOO, H. J. ALTER, G. L. GITNICK, A. G. REDEKER,
R. H. PURCELL, T. MIYAMURA, J. L. DIENSTAG, M. J. ALTER, C. E. STEVENS,
G. E. TEGTMEIER, F. BONINO, M. COLOMBO, W.-S. LEE, C. KUO, K. BERGER,
J. R. SHUSTER, L. R. OVERBY, D. W. BRADLEY, M. HOUGHTON

LA STORIA NATURALE DELLA EPATITE C

Alberti A, et al. *J Hepatol* 2003;38:S104–S108;

FEGATO NORMALE
o
EPATITE MINIMA

INFIAMMAZIONE E
FIBROSI PROGRESSIVA

30%

CIRROSI ED
IPERTENSIONE
PORTALE

SCOMPENSO
VARICI ESOFAGEE
ASCITE
CANCRO
ENCEFALOPATIA

HCV

Fattori di progressione più rapida :

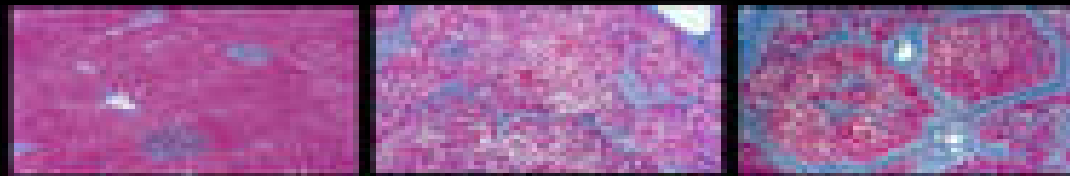
Alcol

HIV

HBV

Diabete/Obesità

VASCULITI
LINFOMI
RESISTENZA INSULINICA
DIABETE TIPO 2
CVD



IL PESO CLINICO ED ECONOMICO DELLA PATOLOGIA HCV

70 milioni di portatori nel MONDO

8-10 milioni in EUROPA

450-750.000 in ITALIA

1° causa di cirrosi/HCC/Trapianto di Fegato nel mondo Occidentale

EUROPA :

143.500 MORTI NEL 2013



67% Cirrosi



291% HCC

ITALIA

12-15.000 Morti/anno

60.000 ricoveri/anno (11 giorni)

Causa/Concausa di patologie extra-epatiche

Vasculiti

ESKD

Linfomi

RI-Diabete tipo 2

CVD

USA : 1506 M USD/y

Francia : 215 M Euro/y

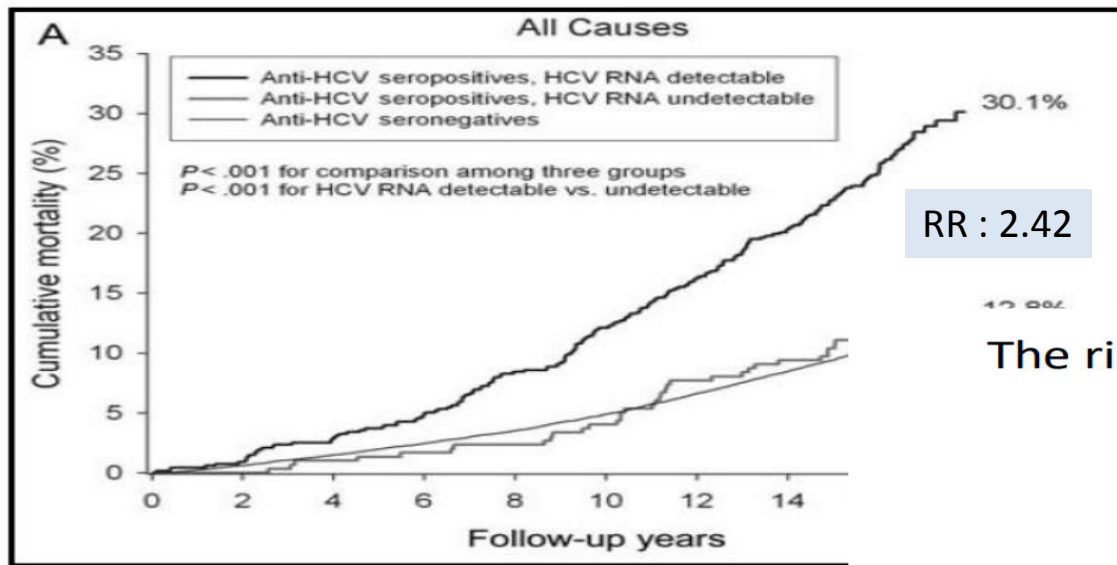
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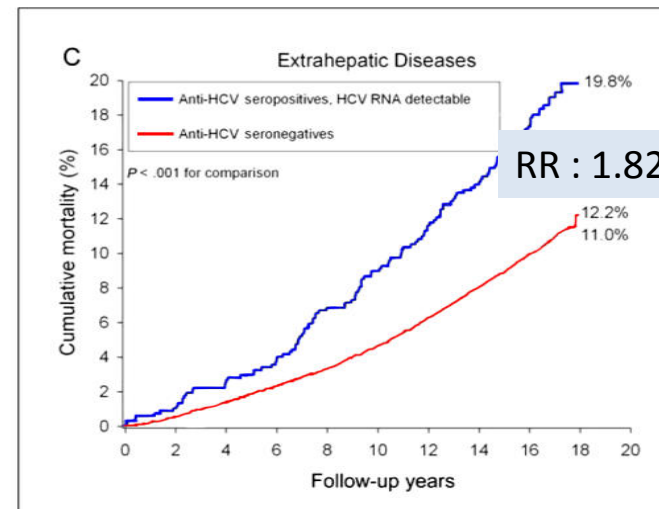
double

16; 388:1081-1

The risk of dying among HCV-infected persons



The risk of dying of non-liver related causes among HCV-infected persons

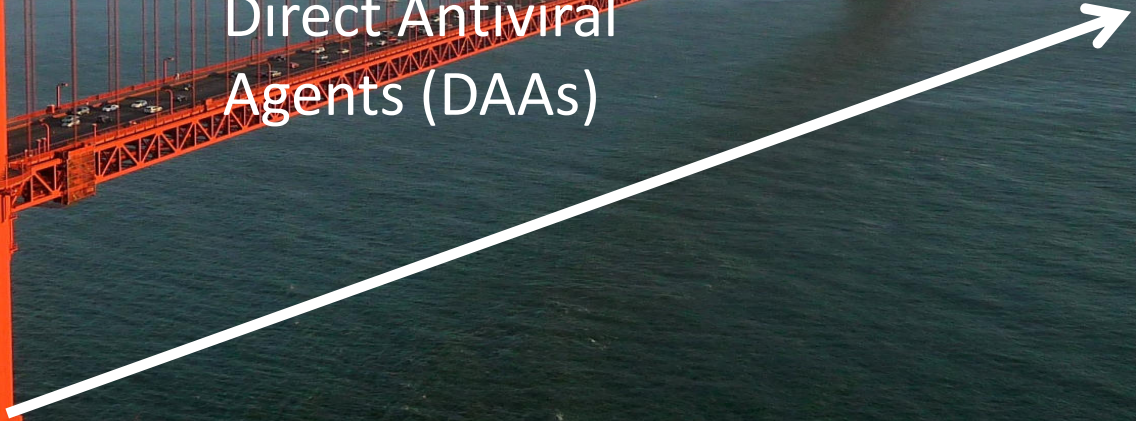


2014 – 2015 : LA SVOLTA EPOCALE NELLA TERAPIA DI HCV

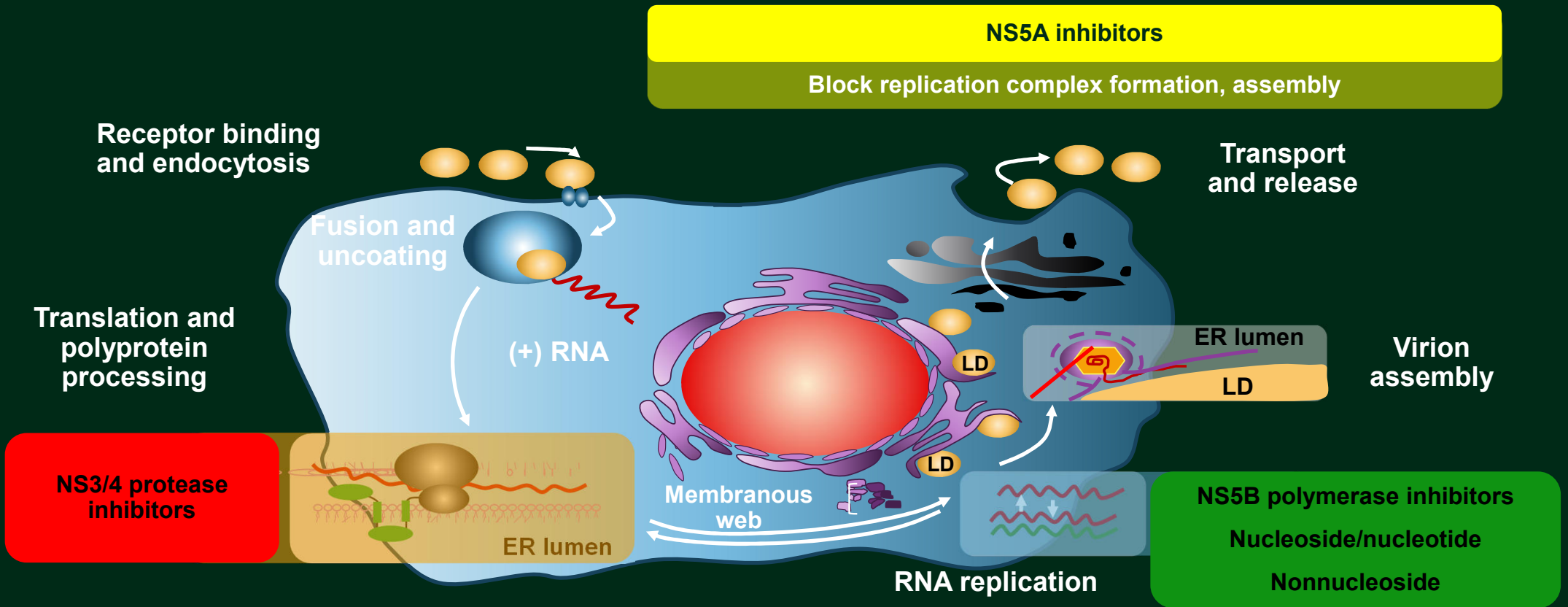
TERAPIA BASATA
SU INTERFERONE

Direct Antiviral
Agents (DAAs)

TERAPIA
IFN-FREE



HCV Life Cycle and DAA Targets



REGIMI IFN-Free x HCV

Non più in uso

	GENOTIPO	DURATA
Sofosbuvir (NS5B) + RBV	2, 3	X 12-24 sett
Sofosbuvir + Simeprevir (PI) (± RBV)	1, 4	X 12-24 sett
Sofosbuvir/Ledipasvir (NS5A) (± RBV)	1, 4, 5, 6	X 8-12-24 sett
Ombitasvir (NS5A)/Paritaprevir (PI) /Ritonavir + Dasabuvir (NNI) (± RBV)	1	X 12-24 sett
Ombitasvir/Paritaprevir/Ritonavir (± RBV)	4	X 12-24 sett
Sofosbuvir + Daclatasvir (NS5A) (± RBV)	PANGENO	X 12-24 sett

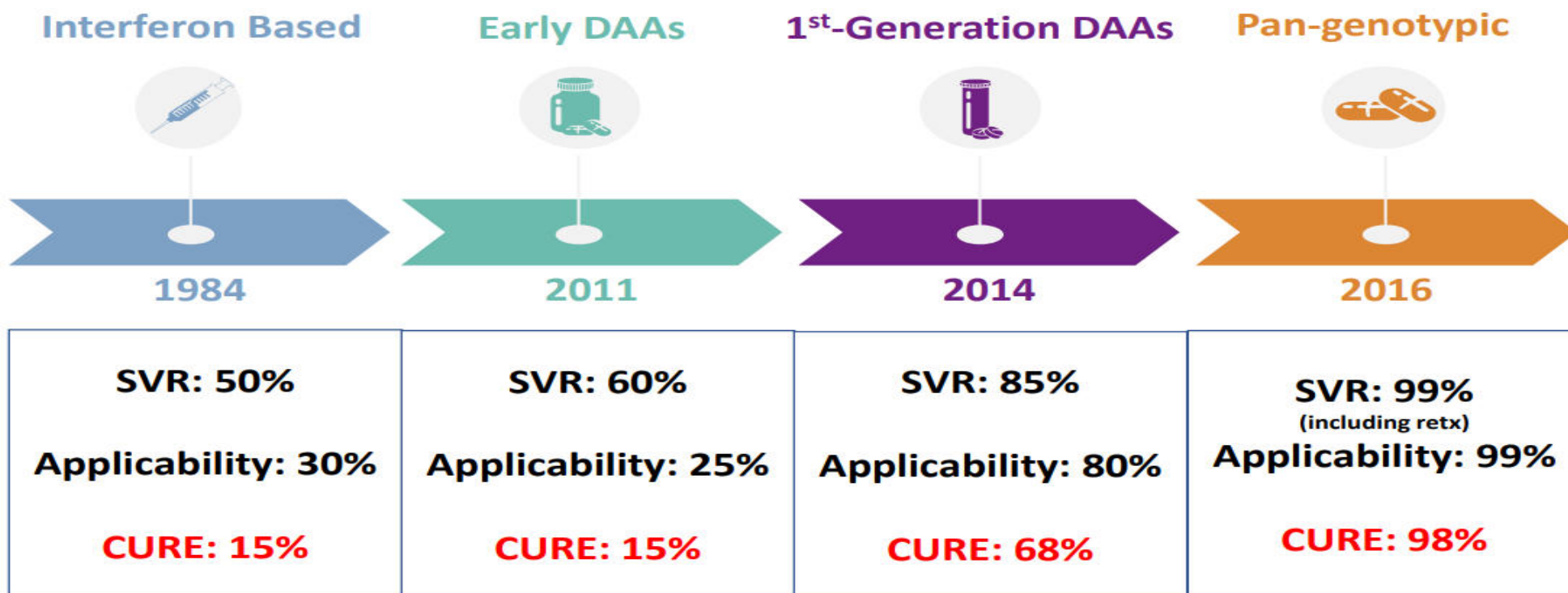
1° LINEA

Grazoprevir (PI) + Elbasvir (NS5A) (± RBV)	1, 4	X 12-16 sett
Sofosbuvir + Velpatasvir (NS5A) (± RBV)	PANGENO	X 12 sett
Glecaprevir (PI) + Pibrentasvir (NS5A) (± RBV)	PANGENO	X 8-16 sett

RITRATTAMENTI DOPO FALLIMENTO 1° LINEA

Sofosbuvir + Velpatasvir (NS5A) + Voxilaprevir (± RBV)	PANGENO	X 12-24 sett
---	---------	--------------

HCV cure rate has evolved substantially over the past 30 years



1. Pawlotsky JM, et al. *J Hepatol* 2016; **62**:S87–99;
 2. Manns M, et al. *Nat Rev Dis Primers* 2017; **3**:1–19.

CRITERI AIFA DI RIMBORSABILITA' DAA 2015-2016

CRITERIO 1 - Pazienti con **cirrosi in classe di Child A o B e/o con HCC con risposta completa** a terapie resettive chirurgiche o loco-regionali non candidabili a trapianto epatico nei quali la malattia epatica sia determinante per la prognosi

CRITERIO 2 - **Epatite ricorrente HCV-RNA positiva del fegato trapiantato** in paziente stabile clinicamente e con livelli ottimali di immunosoppressione

CRITERIO 3 - Epatite cronica con **gravi manifestazioni extra-epatiche HCV-correlate** (sindrome crioglobulinemica con danno d'organo, sindromi linfoproliferative a cellule B)

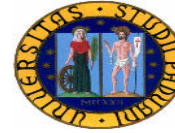
CRITERIO 4 - Epatite cronica con **fibrosi METAVIR F3** (o corrispondente Ishack)

CRITERIO 5 - **In lista per trapianto di fegato** con cirrosi MELD <25 e/o con HCC all'interno dei criteri di Milano con la possibilità di una attesa in lista di almeno 2 mesi

CRITERIO 6 - Epatite cronica **dopo trapianto di organo solido (non fegato) o di midollo** con fibrosi METAVIR ≥ 2 (o corrispondente Ishack)

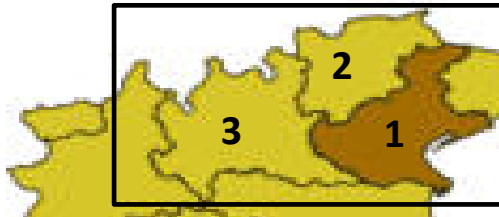


REGIONE DEL VENETO



LA PIATTAFORMA NAVIGATORE

Nuovi AntiVrali per epatite C : Gestione Attraverso Registro degli Esiti



4.925.000	}	Residenti
1.110.000		
10.003.000		

PIATTAFORMA on-line su sistema RedCAP

VENETO :

HUB
SPOKE

119

FLUSSI PAZIENTI in tempo reale : Andamenti e Programmazione Regionale

OTTIMIZZAZIONE e OMOGENEITA' NELLA GESTIONE CLINICA secondo linee di Indirizzo Nazionali e Regionali

VERIFICHE DI APPROPRIATEZZA anche in rapporto a Benchmark Regionali

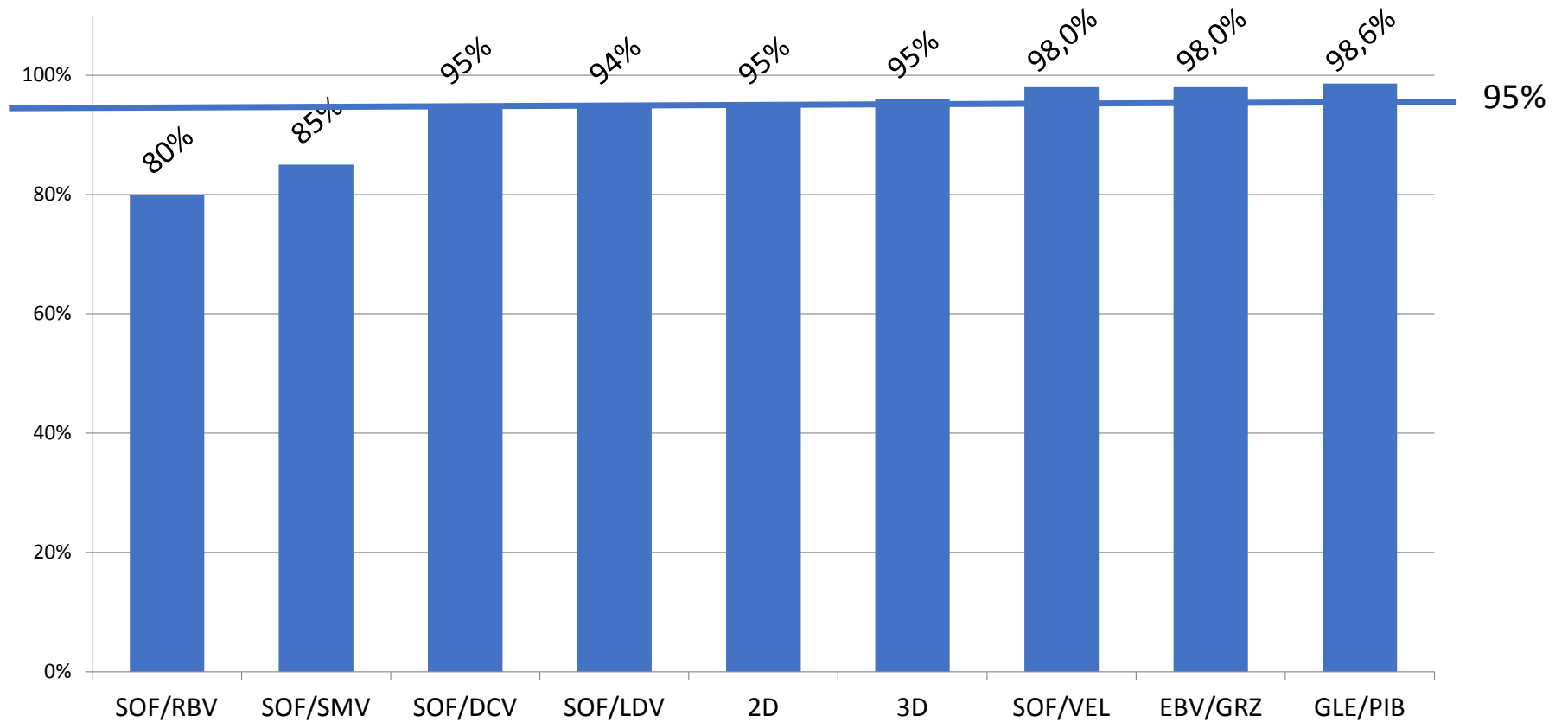
REGISTRAZIONE PROSPETTICA DEGLI OUTCOME

Virologici
Clinici

SICUREZZA ed EFFETTI AVVERSI : collaborazione con Centro Regionale di Farmacovigilanza

SVR 12 IN HCV PATIENTS TREATED IN THE NAVIGATORE PLATFORM data from 7514 patients

ACCORDING TO DAA REGIMEN





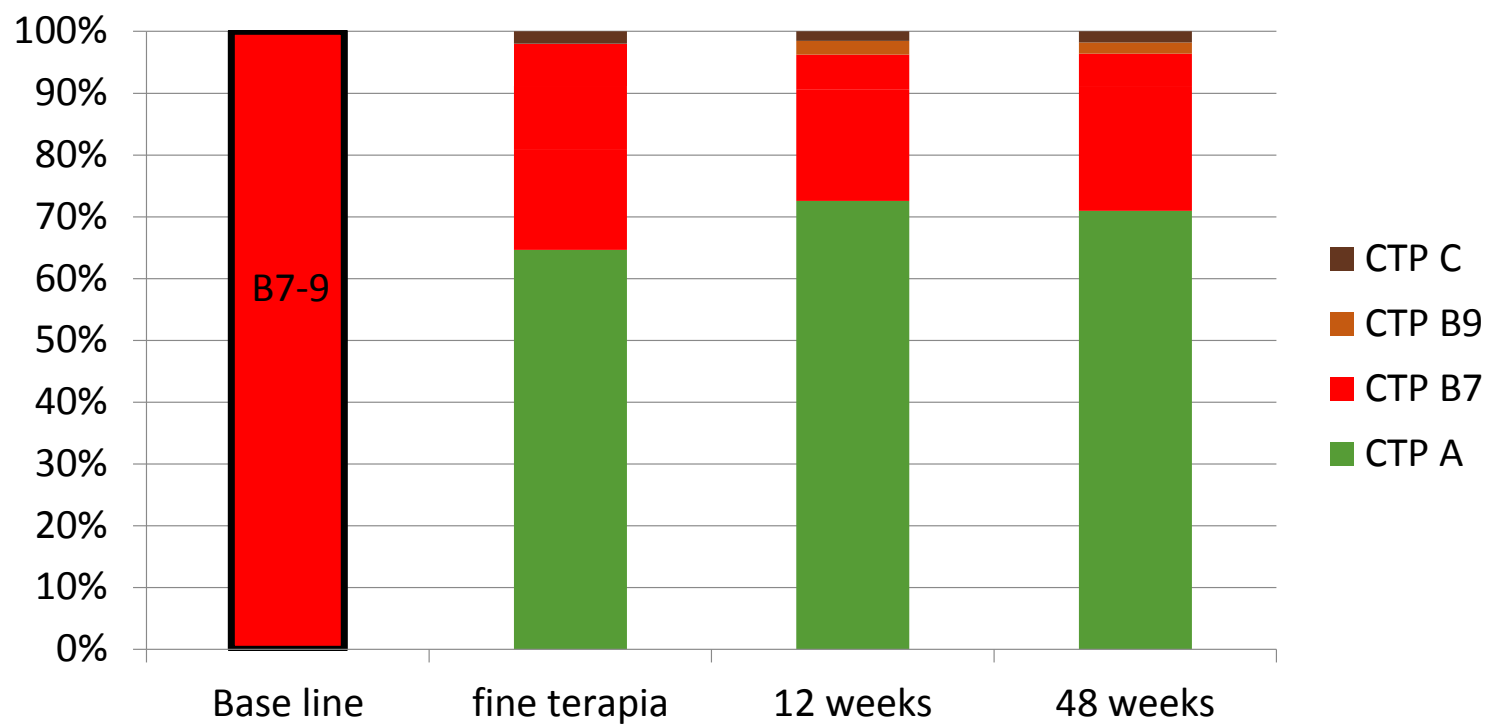
COMPLICANZE REGISTRATE IN PAZIENTI CON CIRROSI CHILD A TRATTATI CON DAAs NEL DATABASE NAVIGATORE DEL VENETO

ESITI	1° ANNO	2° ANNO	3° ANNO	NON TRATTATI
SANGUINAMENTO GI	0.71%/anno	0.24%/anno	0.12%/anno	1.5%/anno
ASCITE	1.9%/anno	0.72%/anno	0.24%/anno	3.0%/anno
SCOMPENSO EPATICO	3.0%/anno	0.9%/anno	0.24%/anno	4.2%/anno
EPATOCARCINOMA	2.4%/anno	0.9%/anno	0.3%/anno	3.0%/anno
DECESSO PER CAUSA EPATICA	0.8%/anno	0.1%/anno	0%/anno	2.0%/anno

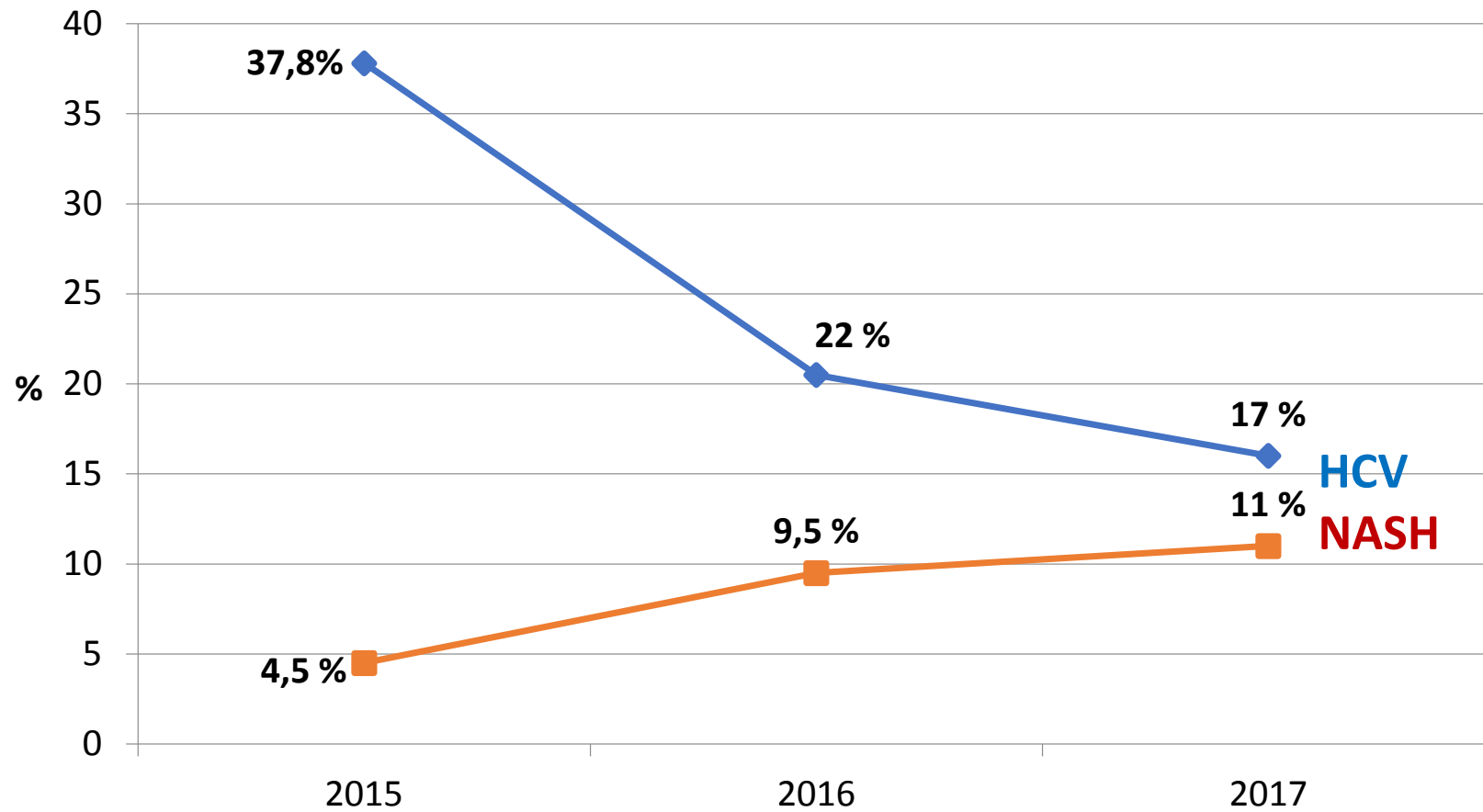


DAAs EFFECTS ON CHILD SCORE

Data from 345 CHILD B CIRRHOTICS

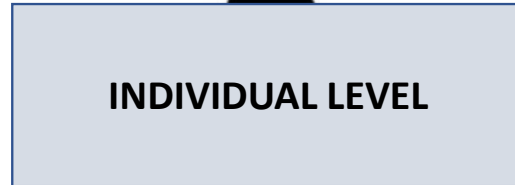


TRAJECTORIES OF WAIT-LISTING FOR LIVER TRANSPLANT BY ETIOLOGY IN PADOVA



Courtesy of P Burra/G Germani

FROM



INDIVIDUAL LEVEL

TO

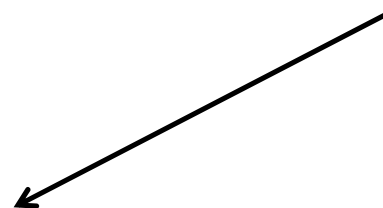


POPULATION LEVEL

TARGET :

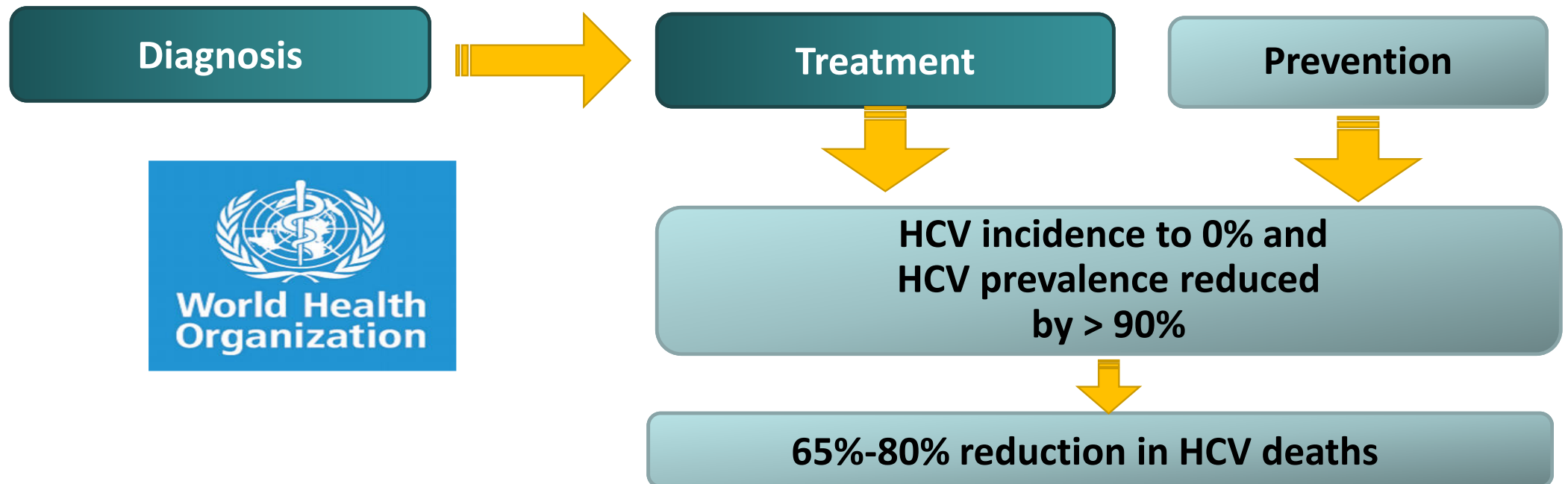


- DISEASE CONTROL
- HCV ELIMINATION
- HCV ERADICATION

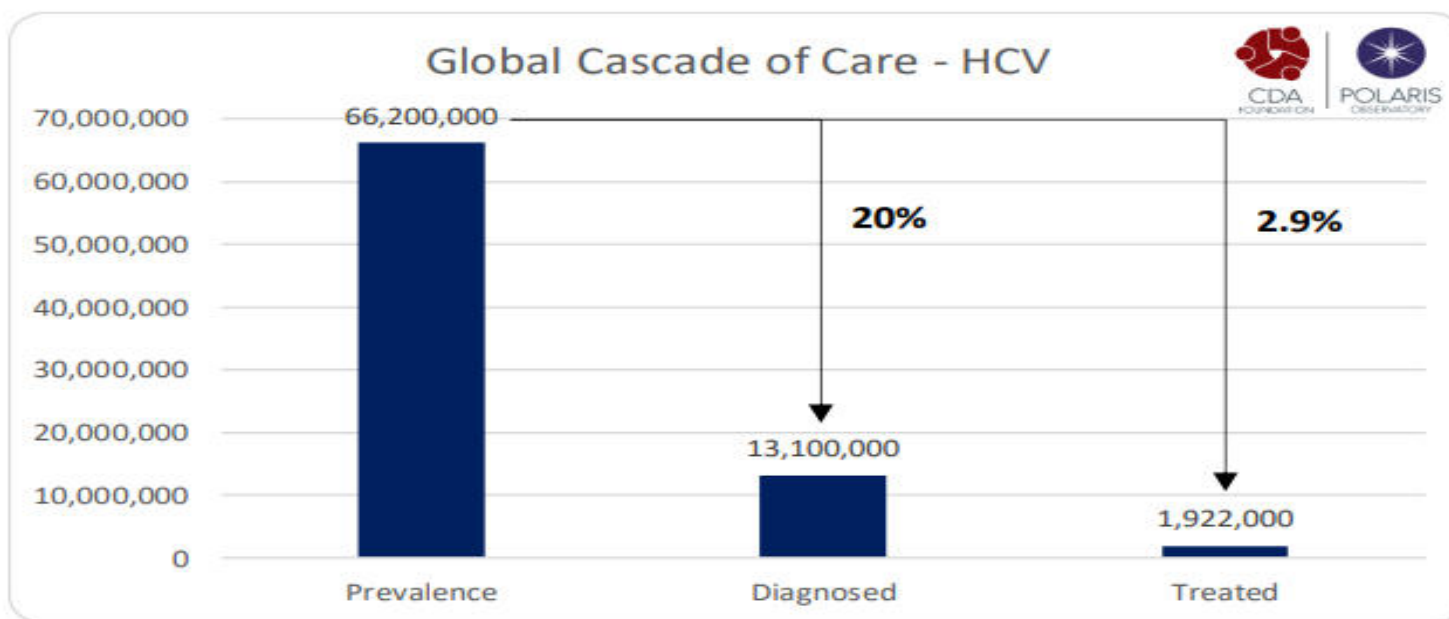


The Goal of Hepatitis C Elimination -

Elimination of HCV infection in the country through identifying **90%** and treating **80%** HCV patients strengthened by effective prevention interventions



80% of all HCV infections remain undiagnosed and more than 97% are untreated in 2018



LA FILIERA PER UNA EFFICACE STRATEGIA DI ELIMINAZIONE DI HCV

**VOLONTA'
POLITICA**

Accesso universale alla terapia

**Finanziamenti dedicati
(non solo farmaci)**

Epidemiologia attuale

**Programmi regionali di microeliminazione
integrata**

Sensibilizzazione ed Educazione

Screening mirati

Semplificazione della diagnosi

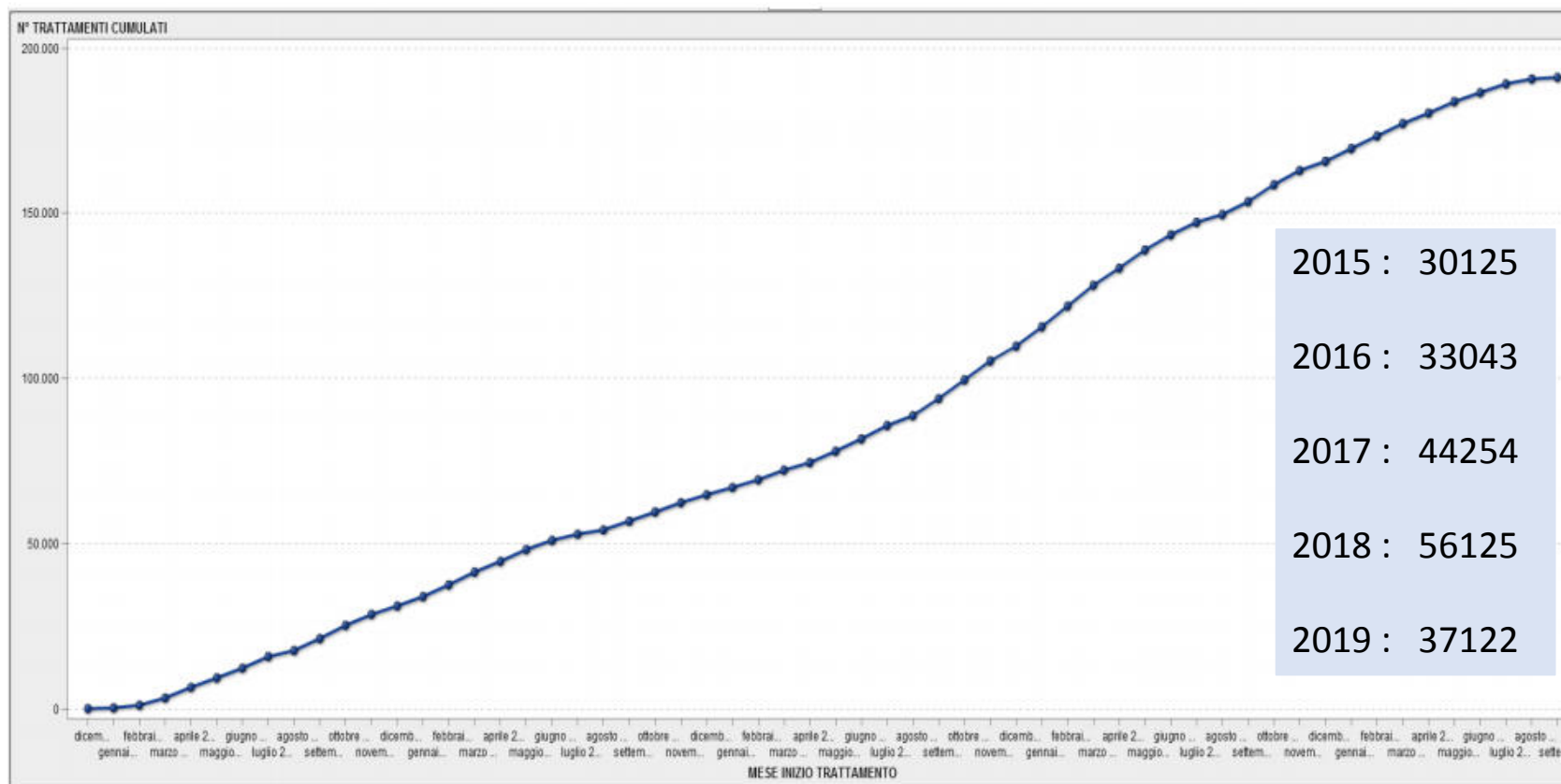
Facilitazione del linkage to care

Nuovi Provider DAA

Prevenzione infezione/reinfezione

**TRATTAMENTO
>7%/ANNO DEL
POOL INFETTI**

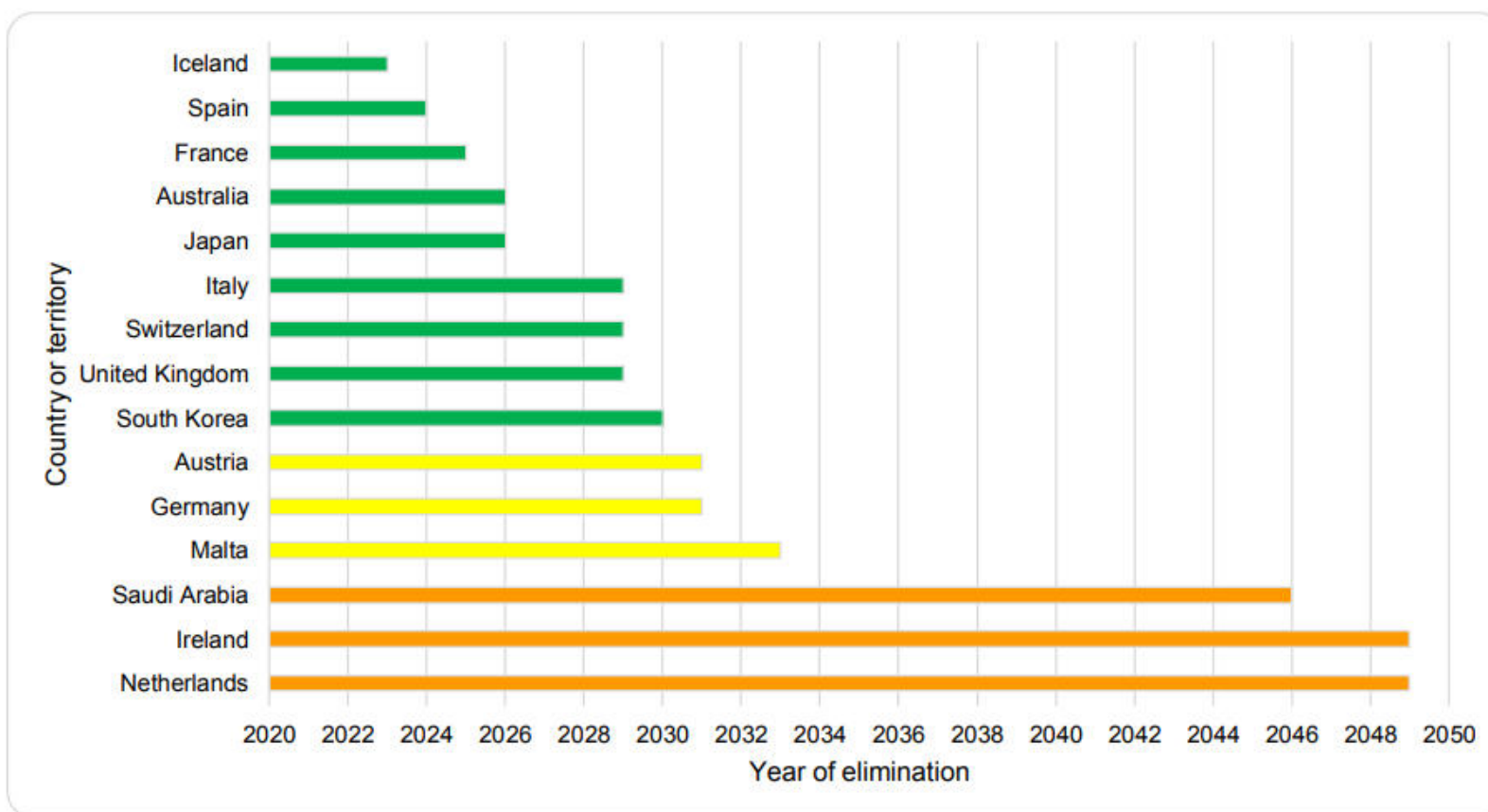
Trend cumulativo dei trattamenti avviati



191.119 «avviati» sono i trattamenti (solo pazienti eleggibili)
 con almeno una scheda di Dispensazione farmaco

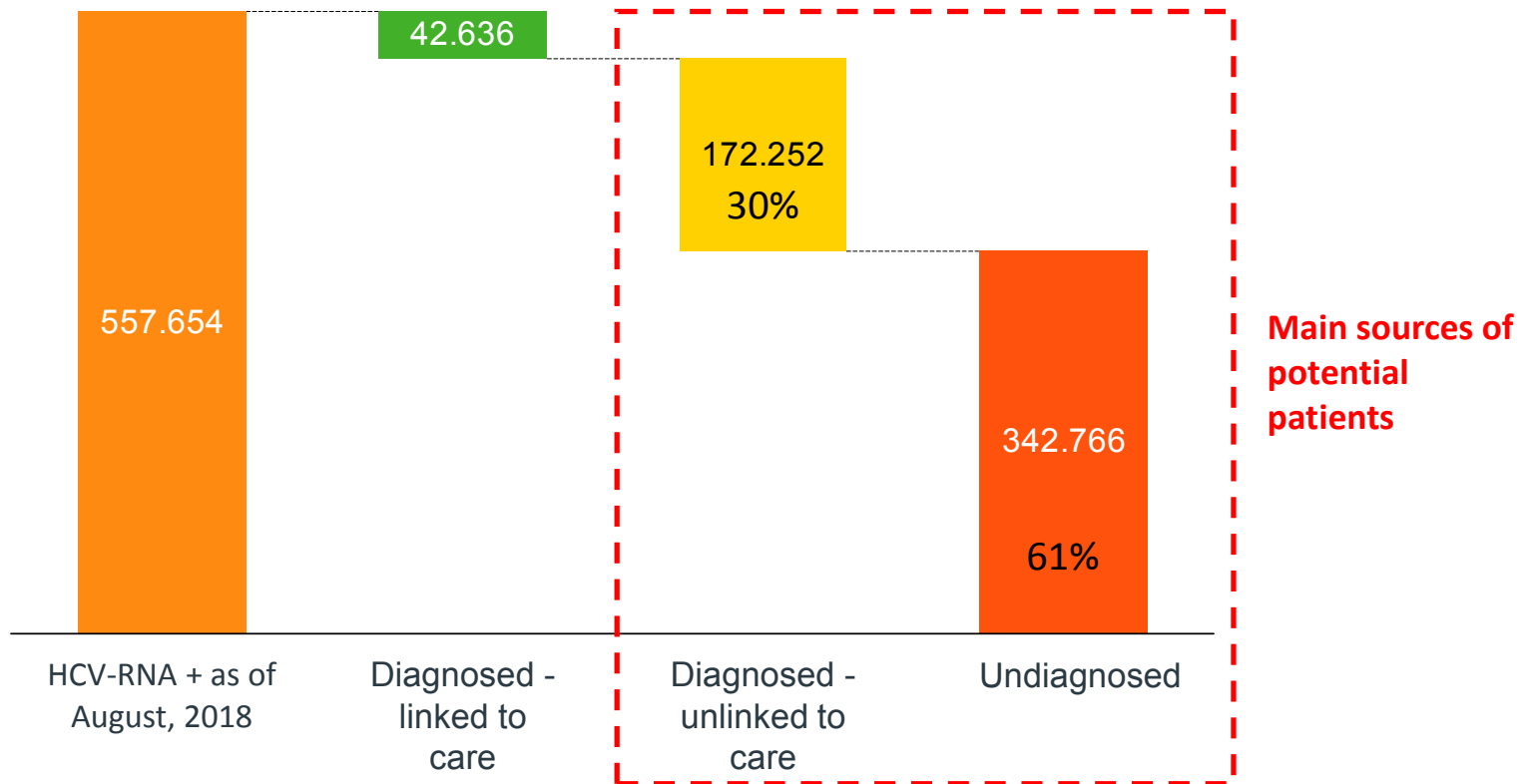


Only 20% of 45 high income countries are forecasted to reach the WHO elimination targets by 2030 and only 33% by 2050



According to our estimations, 172k patients are diagnosed but not under care, and 343k are undiagnosed








Phase 1 results: HCV prevalence split by "link to care" status



Figures calculated by combining expert opinion (distribution among linked-to-care, unlinked-to-care and undiagnosed) and epidemiological model output, and reducing linked-to-care patient number by the number of DAA-treated and healed patients

More than 100k patients are estimated to be drug related, while 230k were infected by glass syringes or transfusions

Patient estimate (considering transmission routes overlap and DAAs treatment)

Transmission route	N. patients ¹ (before DAAs)	DAAs cured patients ²	New infections ³	Actual infected ⁴
 Drug related	113.995	12.564	441	101.871
 MSM with sexual risk practices	39.458	7.990	454	31.922
 Tattoo & piercing	91.120	15.729	497	75.888
 Blood transfusion	153.369	34.024	0	119.345
 Vertical transmission	16.738	3.415	42	13.365
 Glass syringe	142.891	32.933	0	109.958
 Unknown risk factor	136.300	31.661	667	105.306
Total	693.870	138.316	2.100	557.654

1. Epidemiological model output
2. Data from Registri AIFA split by risk factor using model output fibrosis distribution by transmission route
3. Analysis based on bollettino SEIEVA data and expert opinion
4. Column 1 – column 2 + column 3 = current HCV-RNA+ population

Source: QVIA epidemiological model output, Sept. 2018


**THE HCV ICEBERG EMERGED/SUBMERGED RATIO
IS HIGHLY VARIABLE**

A circular illustration of a white iceberg floating in blue water. The iceberg is partially submerged, with a small portion above the surface and a larger portion below. The water is a light blue color, and the sky is a pale blue.

**HCV PATIENTS WITH PROGRESSIVE LIVER
DISEASE**

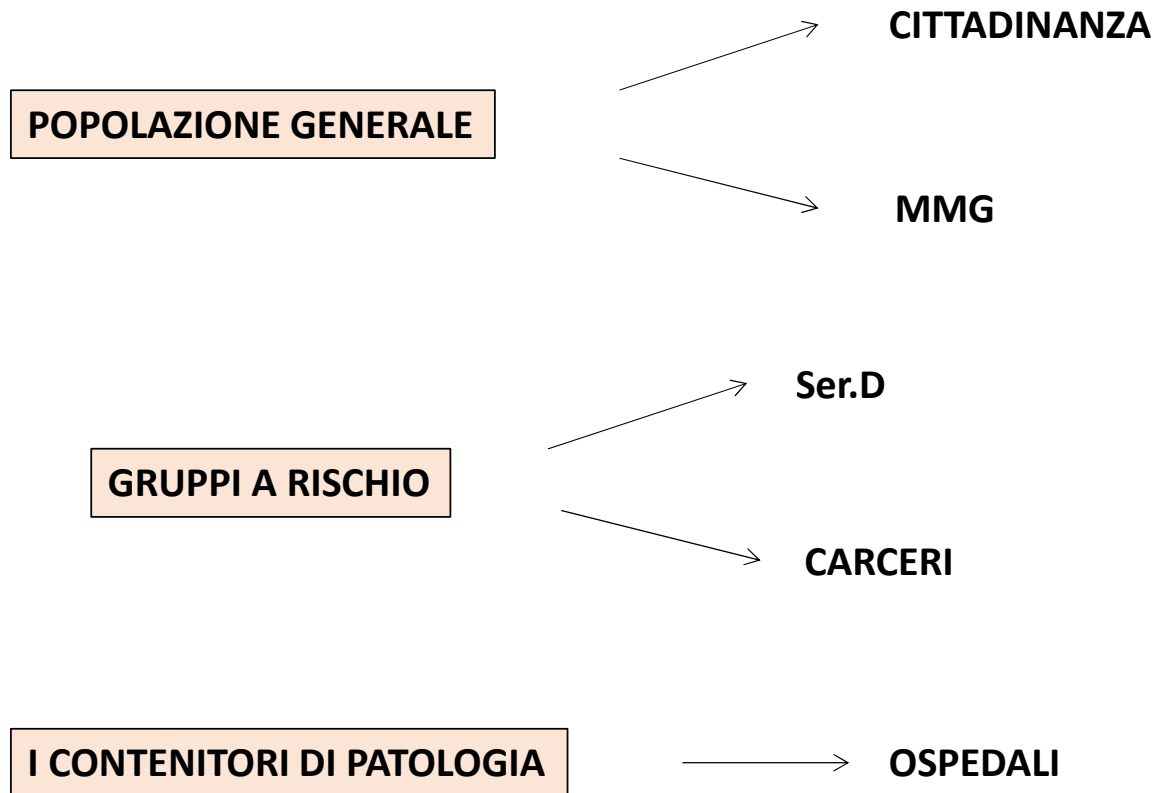
A photograph of a large, jagged white iceberg floating in a deep blue ocean. The iceberg is partially submerged, with a significant portion visible above the water line. The sky is a clear, bright blue.

**HCV IN HIGH RISK BEHAVIOR
GROUPS**

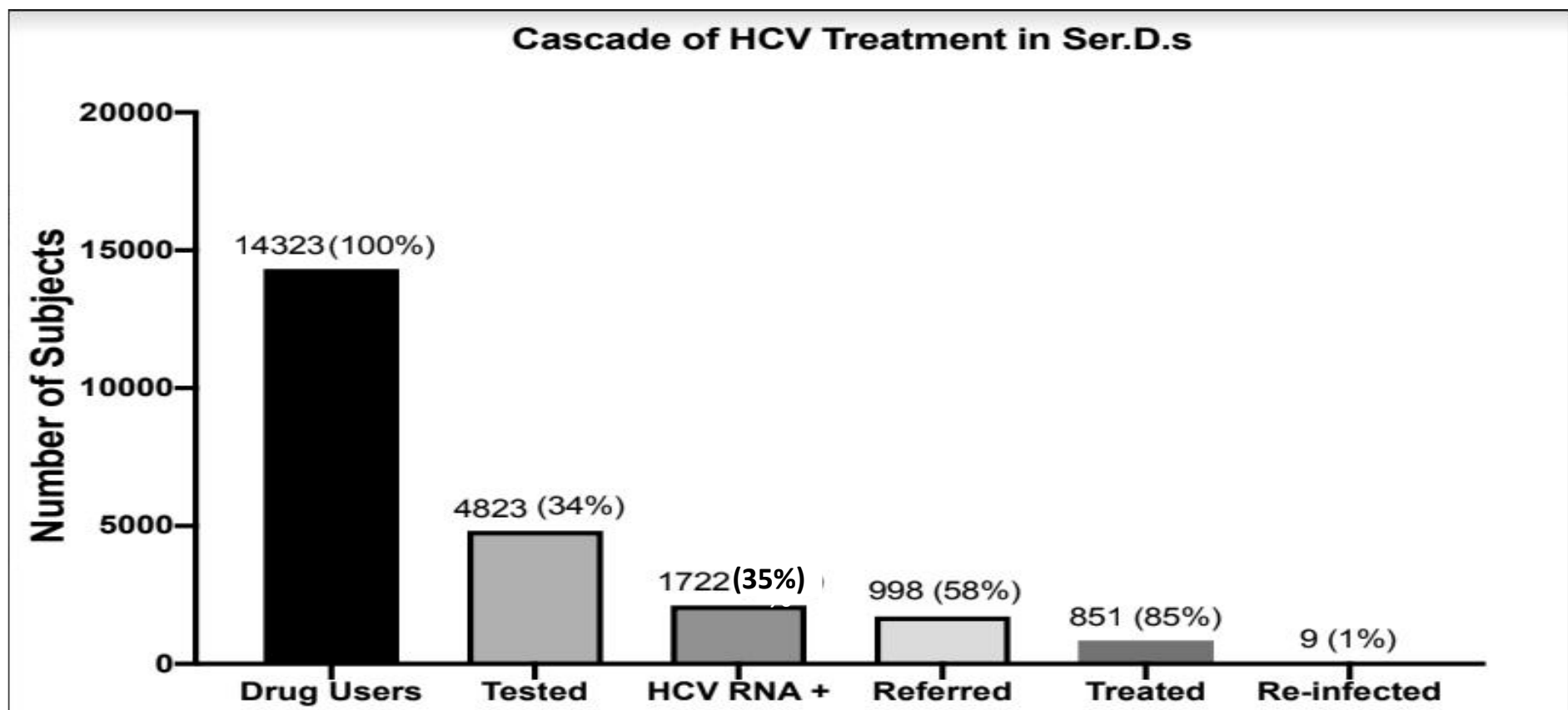
A photograph of a small, white iceberg floating in a dark blue ocean. The iceberg is partially submerged, with a very small portion visible above the water line. The sky is a dark blue.

**HCV IN GENERAL POPULATION WITH NO
SIGNS OF LIVER DISEASE / RISK BEHAVIORS**

GLI AMBITI DI MICROELIMINAZIONE INTEGRATA

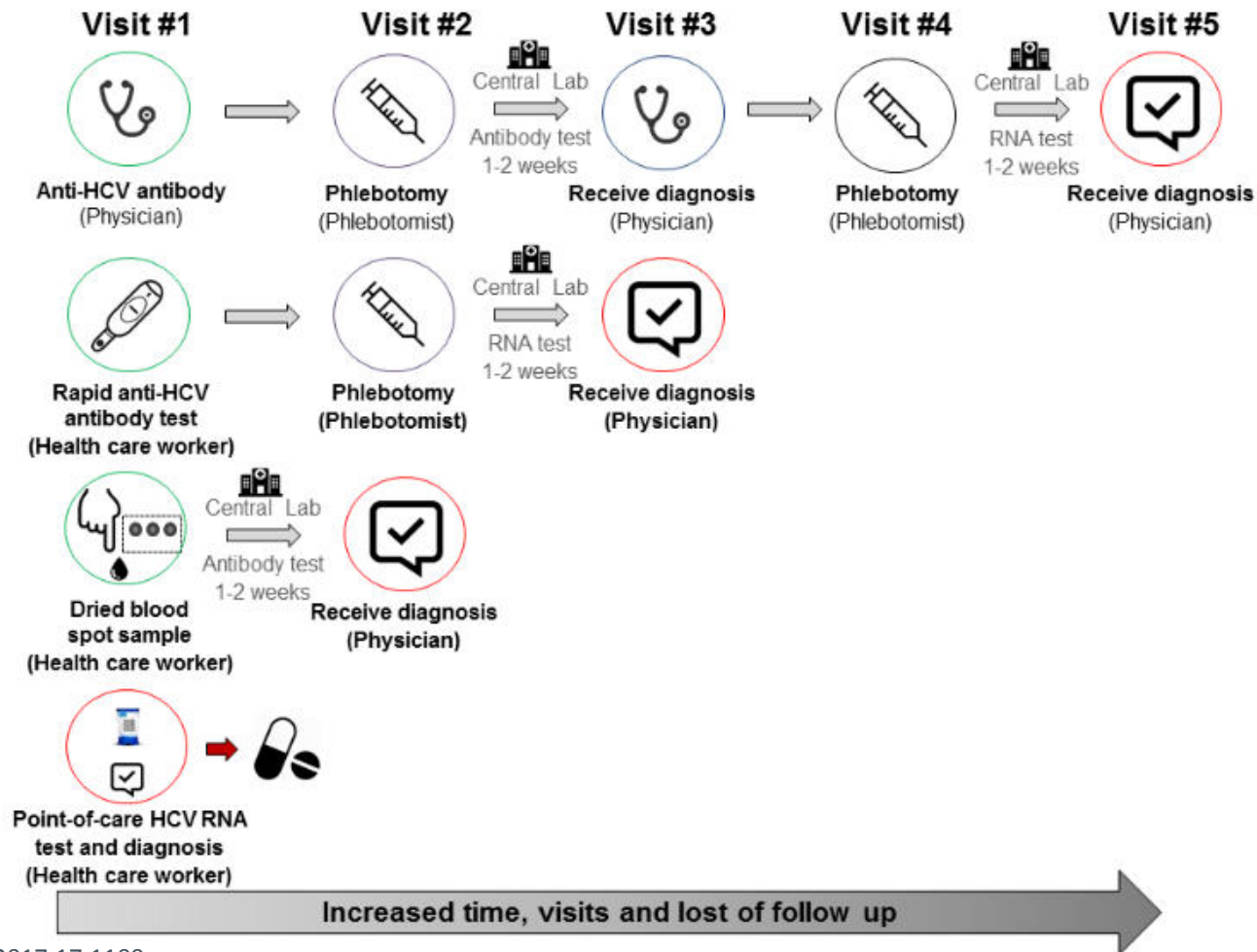


LA FOTOGRAFIA DI HCV NEI Ser.D DEL VENETO



Cortesia Dott. Felice Nava

Moving Toward a Single-Visit Hepatitis C Diagnosis

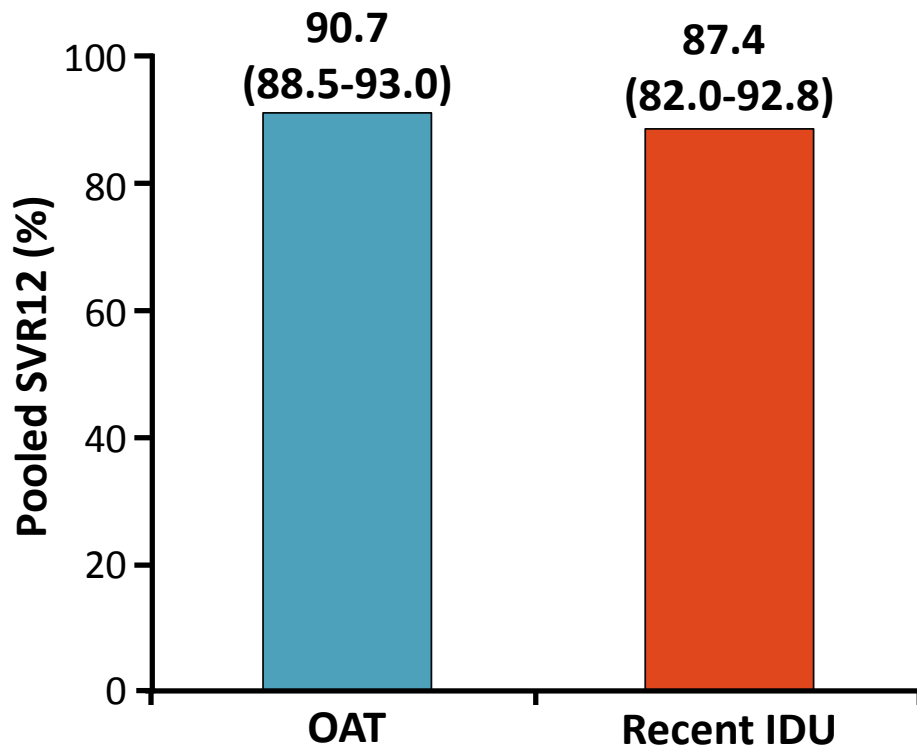


Fibrosis Assessment Is Essential in ALL Patients, and Simplified Tools Are Available

- Presence of cirrhosis affect regimen, and post-SVR HCC surveillance
- **Transient elastography - FIBROSCAN**
 - > 12.5 KPa = cirrhosis
- **Serum tests**
 - **APRI (AST/PLTs) and FIB-4 (AGE/AST/PLTs); can be done anywhere by any provider**
 - Very good **negative predictive value—to rule out cirrhosis**
- Liver biopsy rarely needed



HCV DAA Therapy Is Effective Among PWID, Even in the “Real-World”



Recent IDU

Study	SVR, % (95% CI)
Bielen 2017	83.3 (60.8-94.2)
Boglione 2017	93.9 (89.1-96.6)
Boscaillou 2017	80.4 (73.0-86.2)
Conway 2017	96.7 (88.8-99.1)
Grebely 2018	94.2 (87.9-97.3)
Mazhnaya 2017	64.0 (44.5-79.8)
Milne 2017	87.4 (80.2-92.2)
Valencia 2017	74.4 (59.8-85.1)
Overall	87.4 (82.0-92.8)

- In meta-regression, clinical trials significantly associated with higher SVR rates vs observational studies
 - aOR: 2.18 (95% CI: 1.27-3.75; $P = .006$)
- Difference due to loss to follow-up, not virologic failure



Who Can Treat HCV Infection?

Providers



Task shifting

- Specialists
- Drug and alcohol specialist
- Primary care providers
- Nurses
- Pharmacists
- Peer support workers
- Others

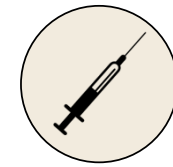
- 3-hr education and training
- Overall SVR : 87%
- **No difference in SVR rate by provider type**

- Nurses: 90%
- PCPs: 88%
- Specialists: 85%

Settings



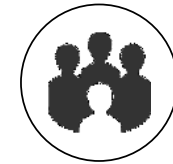
Sexual health clinics



SSP



Drug and alcohol clinics



FQHCs



Primary care clinics



Pharmacies



Prisons

HCV Prevention Among PWID: Harm Reduction and Drug User Health

OAT (Methadone/Buprenorphine)

Country or Region	No. of Studies	RR	95% CI
Australia	3	0.42	0.25-0.72
North America	4	0.57	0.42-0.77
Europe	5	0.43	0.27-0.68
Overall	12	0.51	0.40-0.63

50% reduction in risk

OAT + High Coverage SSP

Study	Unadjusted RR	95% CI
Bruneau 2015	0.63	0.37-1.07
Hope 2011	0.17	0.02-1.54
Palmateer 2014	0.24	0.10-0.59
Van Den Berg 2007	0.15	0.06-0.40
Overall	0.29	0.13-0.65

71%
reduction
in risk

OAT + Low Coverage SSP

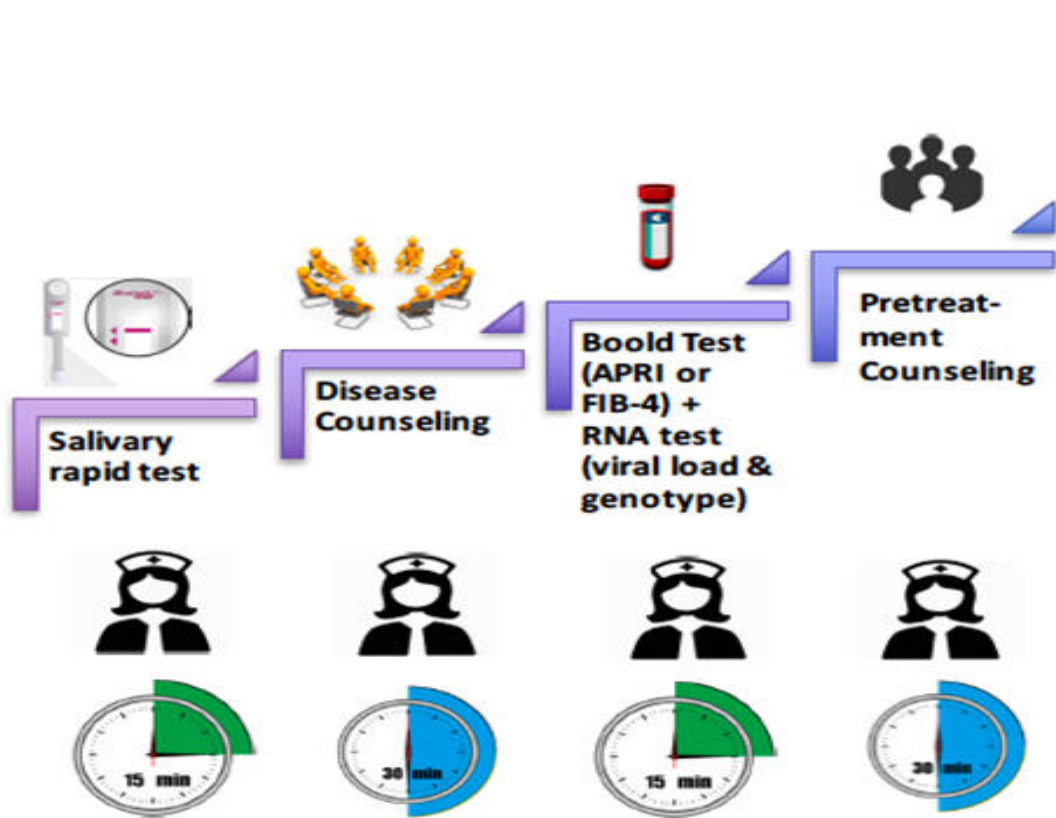
Study	Unadjusted RR	95% CI
Hope 2011	1.08	0.31-3.82
Palmateer 2014	0.48	0.24-0.95
Van Den Berg 2007	1.04	0.53-2.05
Overall	0.76	0.44-1.33

24%
reduction
in risk

LA STRADA PER LA ELIMINAZIONE DI HCV E' ANCORA LUNGA E DIFFICILE



PHASE 1: DAY 1



PHASE 2: DAY 2

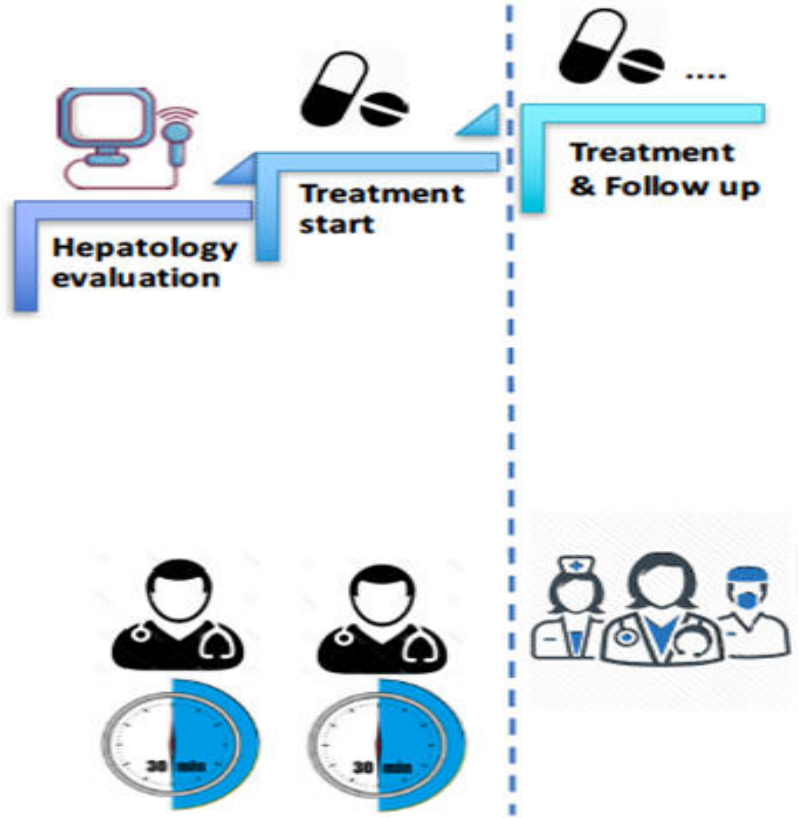


Fig. 1. Fasi del point of care all'interno del Ser.D. e presso le Carceri

HCV Reinfection Rates After SVR Among PWIDs

3.81/100 PY
(95% CI: 2.51-5.80)

- With OAT (methadone/
buprenorphine)
- Meta-analysis of 25 studies

5.86/100 PY
(95% CI: 3.96-8.66)

- With recent IDU
- Meta-analysis of 28 studies