WEBINAR SERIES | SESSION 2

PRACTICAL EDUCATION ON BLEEDING DISORDERS

Knowledge for All

Medical educational webinar series on global topics surrounding bleeding disorders.

TUESDAY JULY 27, 2021, 8–10 A.M. EDT

English with simultaneous translation into Arabic, French, Russian and Spanish.

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WELCOME

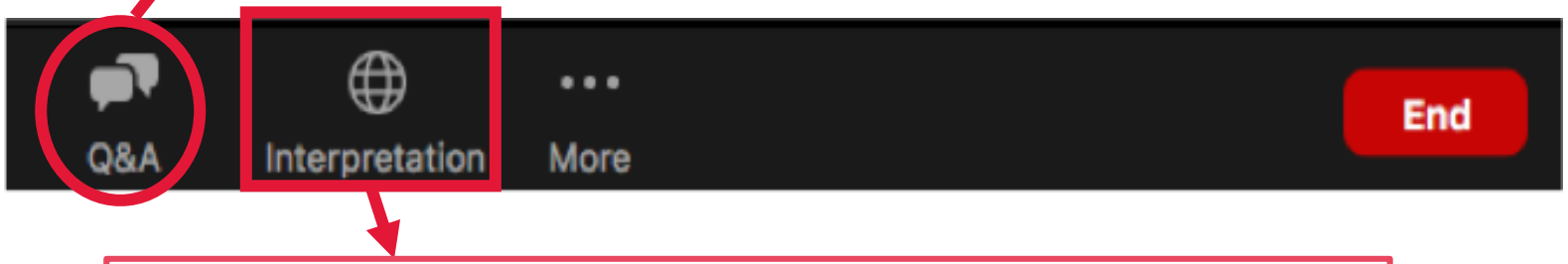
GLENN PIERCE, MD PhD

WFH VICE PRESIDENT, MEDICAL

QUESTIONS AND TRANSLATION

FOR COMPUTERS OR TABLETS

Please submit your questions in the Q&A box



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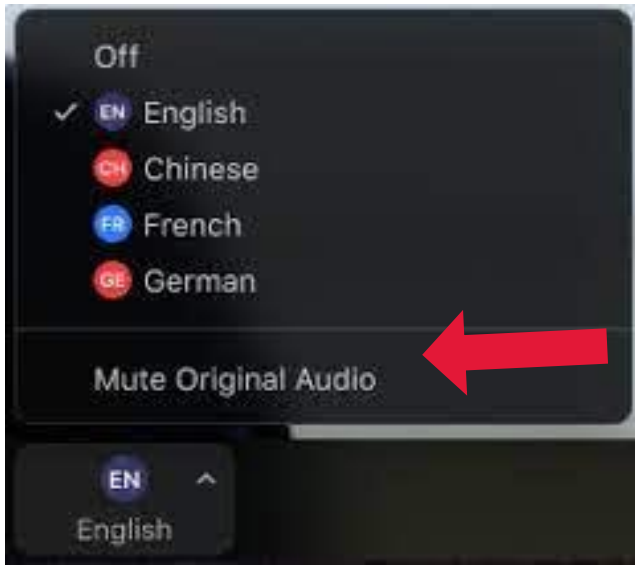

Option to mute the original English audio

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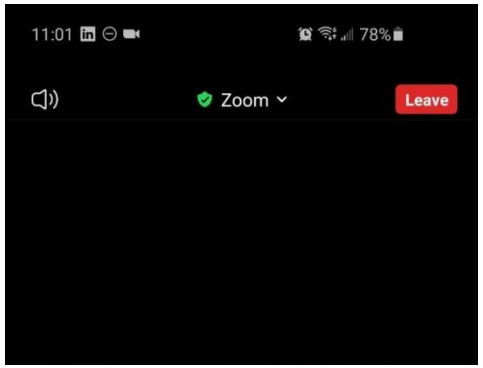
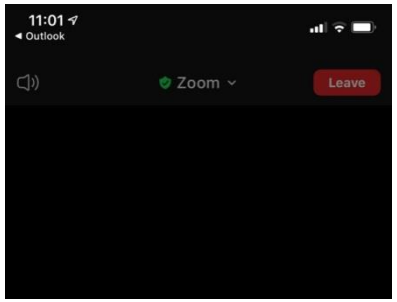
QUESTIONS AND TRANSLATION

FOR MOBILE PHONES





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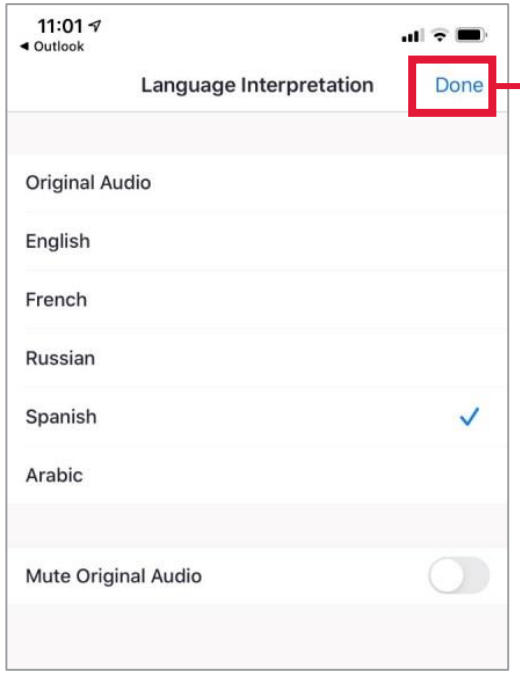

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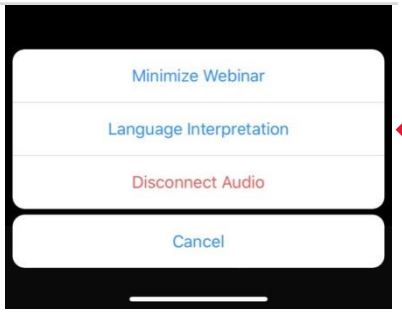

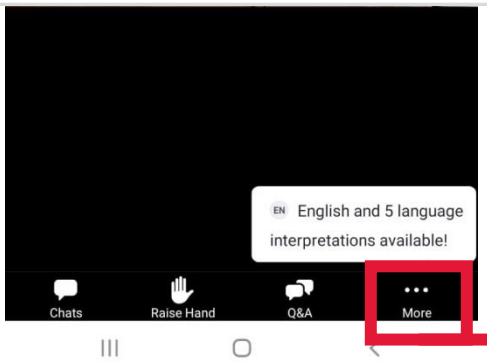

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AGENDA

1. Opening & welcoming remarks
2. Gene Therapy Updates from ISTH 2021
3. Liver Health & Hemophilia: Why does it still matter?
4. Q&A
5. VWD Highlights at ISTH 2021
6. Women with Bleeding Disorders: Why they deserve more attention
7. Q&A
8. Prophylaxis with Limited Resources: Achievement and Expectations
9. Closing remarks

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SPEAKERS

Steve Pipe, MD
Professor of Pediatrics and Pathology
U.S.A.

Heiner Wedemeyer, MD
Professor, Hannover Medical School
Germany

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Gene Therapy Updates from ISTH 2021

Steve Pipe, MD

Professor of Pediatrics and Pathology
U.S.A.

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THANK YOU

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Liver Health and Hemophilia: Why does it still matter?

Heiner Wedemeyer
Dept. of Gastroenterology, Hepatology & Endocrinology
Hannover Medical School Germany

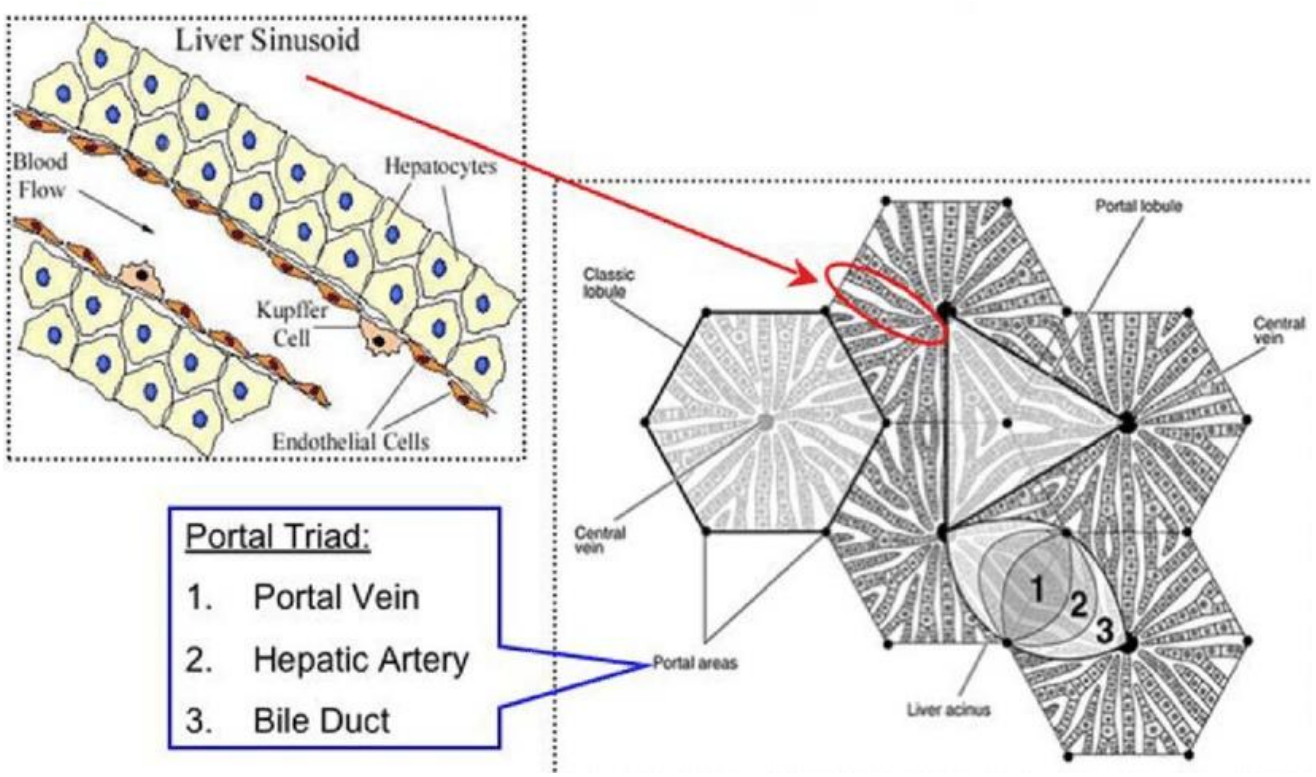
GHE Gastroenterology Hepatology Endocrinology

MHH Medizinische Hochschule Hannover

Disclosure and potential conflicts of interest

Shareholder	No relevant conflicts of interest to declare
Grant / Research Support	Abbott, Abbvie, Gilead, Roche, MYR GmbH
Consultant	Abbvie, Aligos, BMS, Dicerna, Eiger, Falk, Gilead, Janssen, Intercept, Merck / MSD, Merz, MYR GmbH, Norgine, Roche
Employee	No relevant conflicts of interest to declare
Paid Instructor	No relevant conflicts of interest to declare
Speaker bureau	Falk, MSD, Abbvie
Other	Speaker: Pfizer

Liver architecture and cell types in the liver



- Hepatocytes
- Stellate cells
- Endothelial cells
- Cholangiocytes
- Immune cells incl. Kupffer cells
- Oval cells (stem cells)

Liver parameters

Inflammation („hepatitis“): **ALT, AST, (IgG)**

Cholestasis: **alkaline phosphatase, gGT, bilirubin**

Synthesis: **INR, albumin, cholinesterase**

Detoxification: **bilirubin, NH3**

Fibrosis / portal hypertension: **platelets, AST/ALT ratio**

Liver cancer / cholangiocarcinoma: **AFP, AFP-L3, DCP, CA-19-9**

Liver toxicity

Hepatitic pattern: **ALT> AST > AP/gGT**

Cholestatic pattern: **AP/gGT >ALT/AST**

Steatosis: **cholinesterase ↑, ultrasound bright liver, CAP-Score**

Acute ischemic pattern: **AST>ALT, GLDH↑**

Acute Liver failure: **AST > ALT, bilirubin ↑, INR↓**

Liver work-up

- Ultrasound
- Liver elastography
- Steatosis assessment
- Blood flow
- Non-invasive fibrosis markers

AAV-based Gene Therapy of the Liver

Acute toxicity

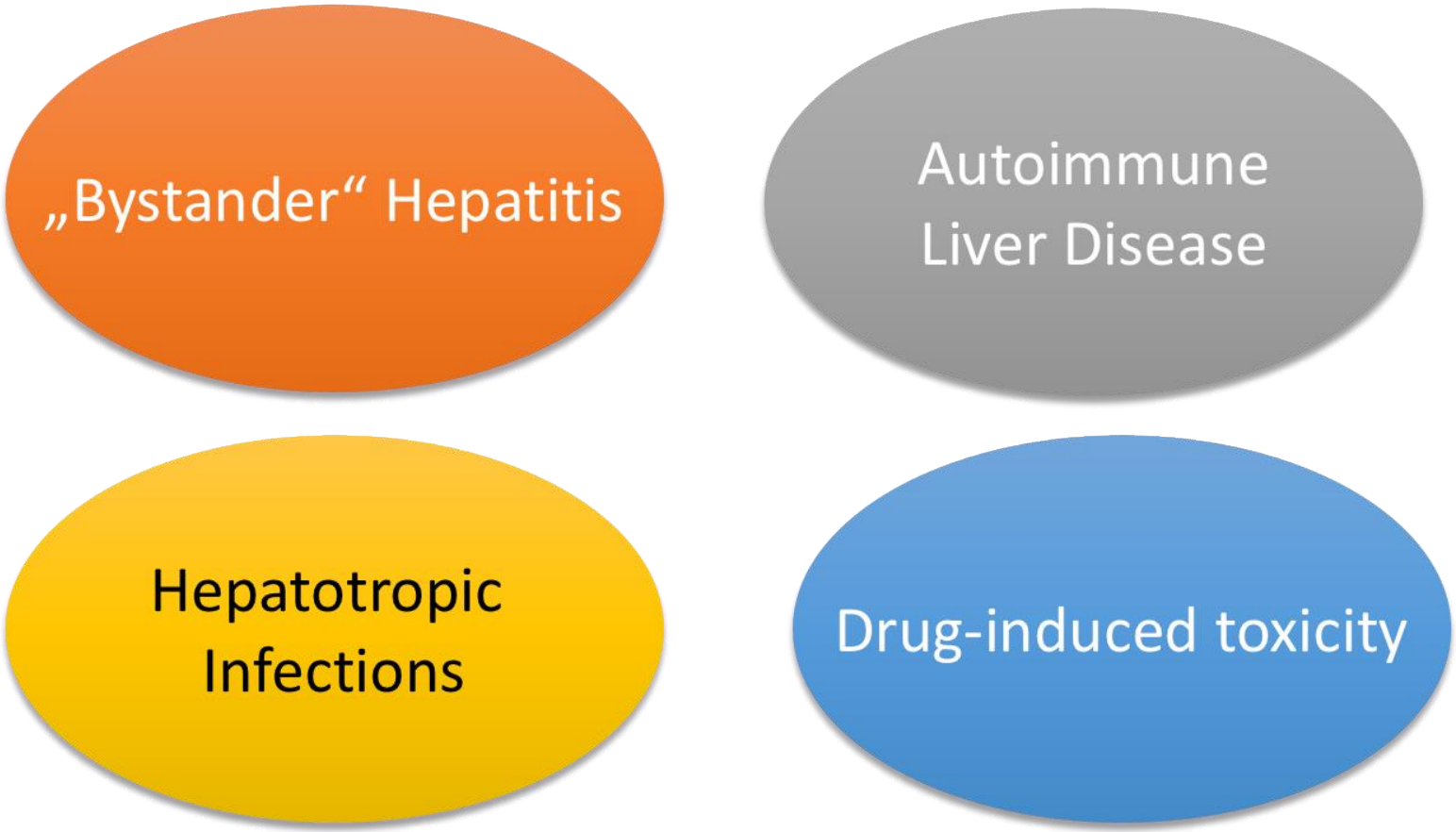
Long-term safety

comorbidities

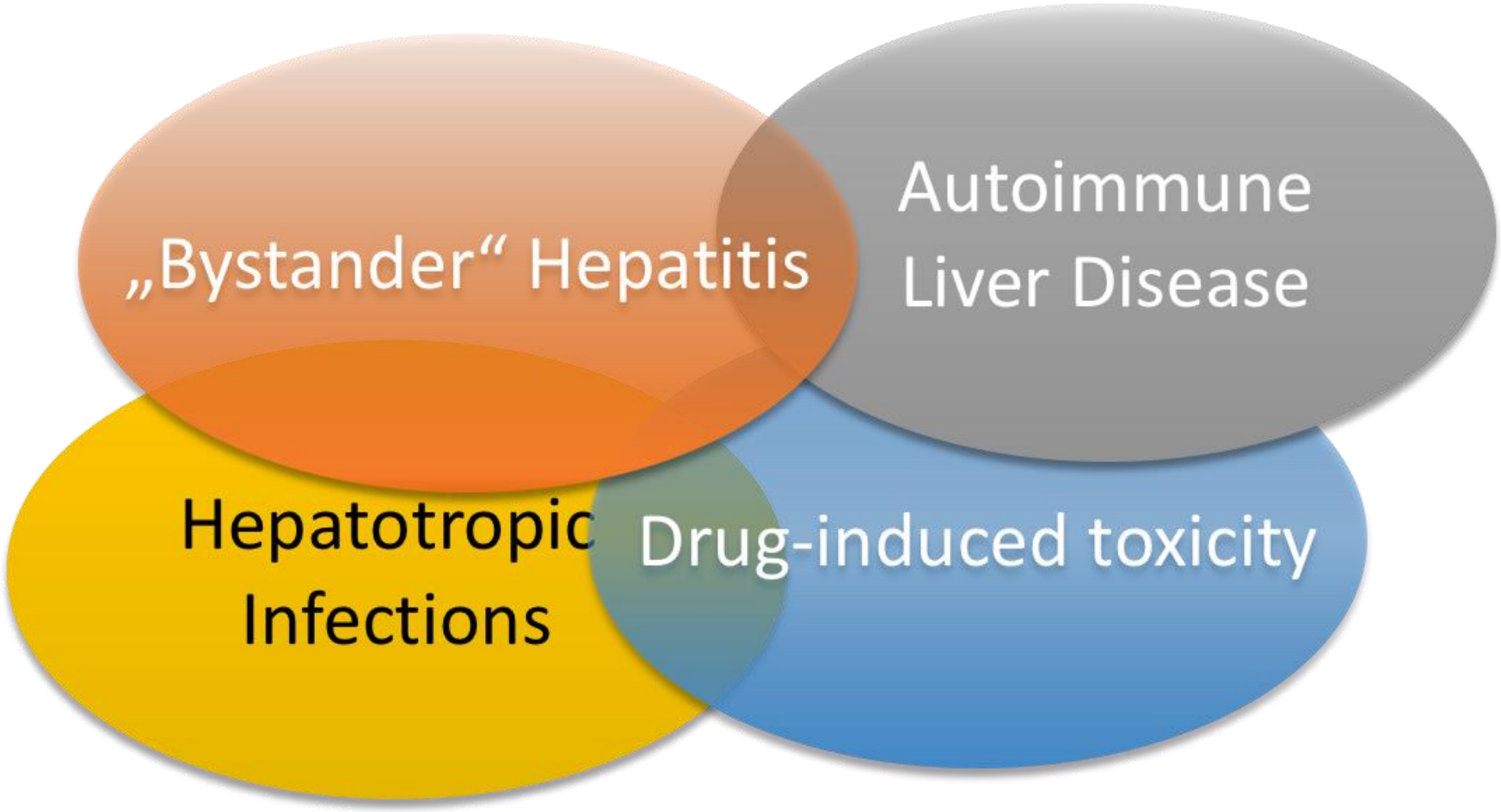
Monitoring: Lab values, ultrasound, liver elastography

AAV vectors and different liver cell populatons

Elevated Liver Enzyms (Acute hepatitis)



Differential Diagnosis



Bystander Hepatitis

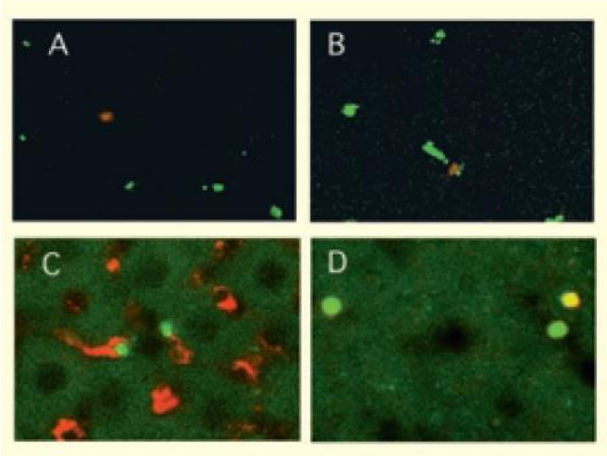
„Bystander“ Hepatitis

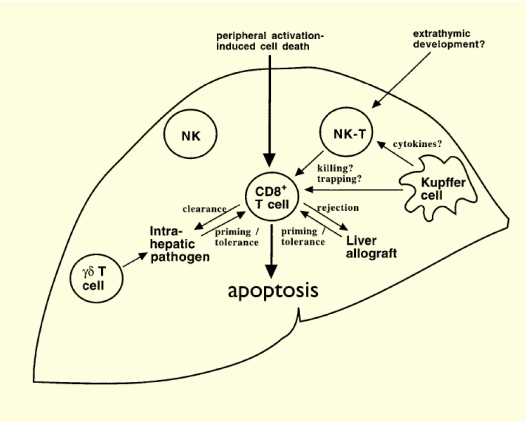
Autoimmune Liver Disease

Hepatotropic Infections

Drug-induced toxicity

Effector-T-cells undergo apoptosis in the liver





N. Crispe et al., Immunological Reviews 2000

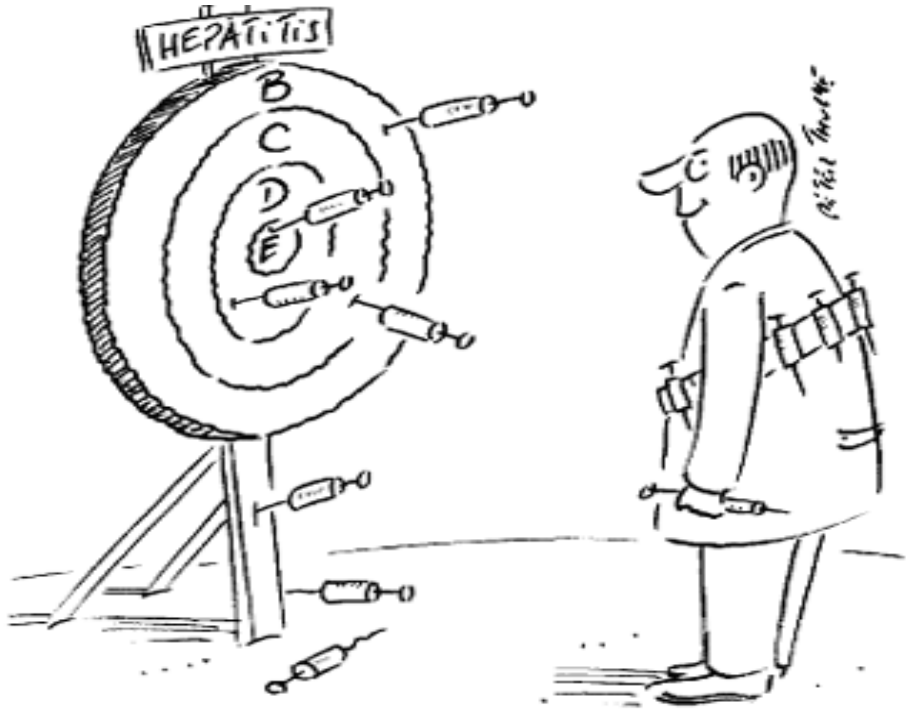
Viral Hepatitis

„Bystander“ Hepatitis

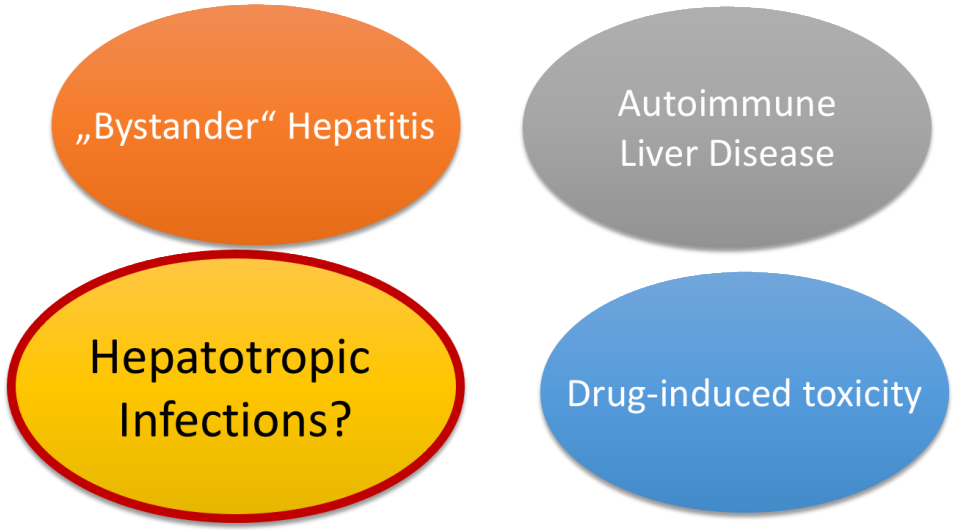
Autoimmune Liver Disease

Hepatotropic Infections?

Drug-induced toxicity



Viral Hepatitis



Science
AAAS

EUROPE'S NEW HEPATITIS PROBLEM

Many get infected with hepatitis E, and a few get very sick. How can the virus be stopped?

Autoimmune Liver Disease

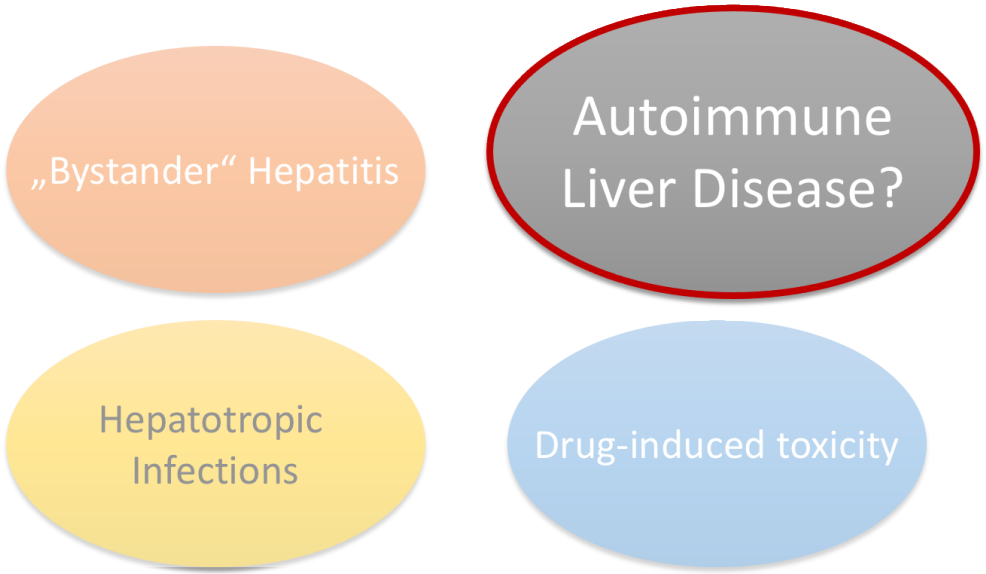


Table 2. Simplified Diagnostic Criteria for Autoimmune Hepatitis

Variable	Cutoff	Points
ANA or SMA	≥1:40	1
ANA or SMA	≥1:80	
or LKM	≥1:40	2*
or SLA	Positive	
IgG	>Upper normal limit	1
	>1.10 times upper normal limit	2
Liver histology (evidence of hepatitis is a necessary condition)	Compatible with AIH	1
	Typical AIH	2
Absence of viral hepatitis	Yes	2
		≥6: probable AIH ≥7: definite AIH

*Addition of points achieved for all autoantibodies (maximum, 2 points).

Hennes et al., Hepatology 2008

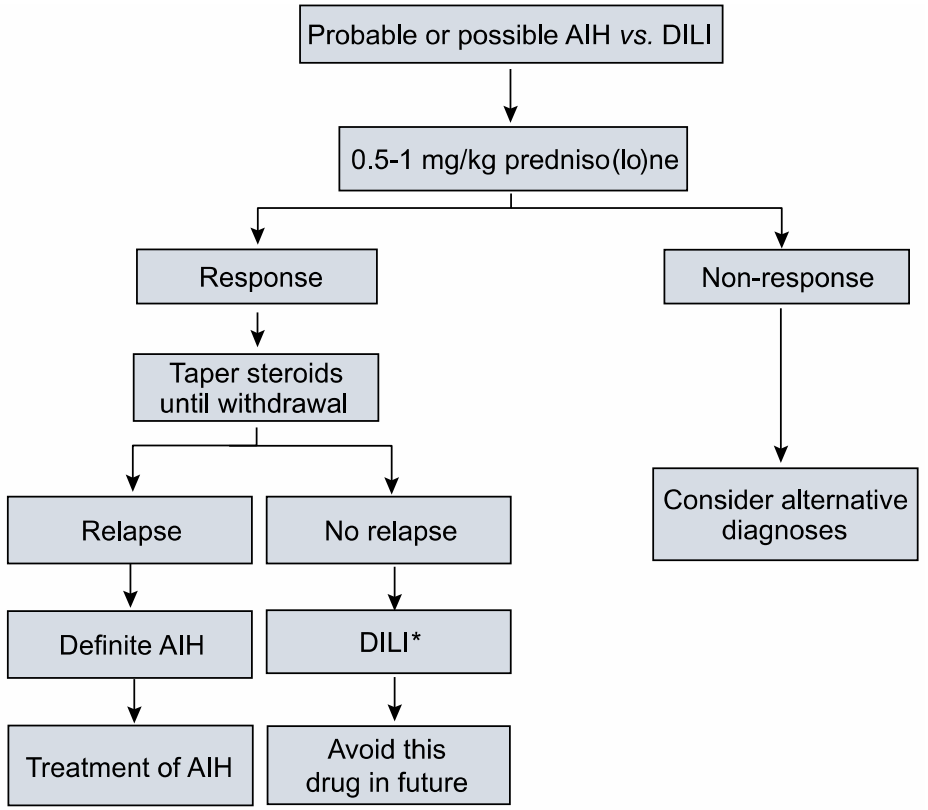
Drug-Induced Liver Disease

„Bystander“ Hepatitis

Autoimmune Liver Disease

Hepatotropic Infections

Drug-induced toxicity?



Clinical Practice Guidelines

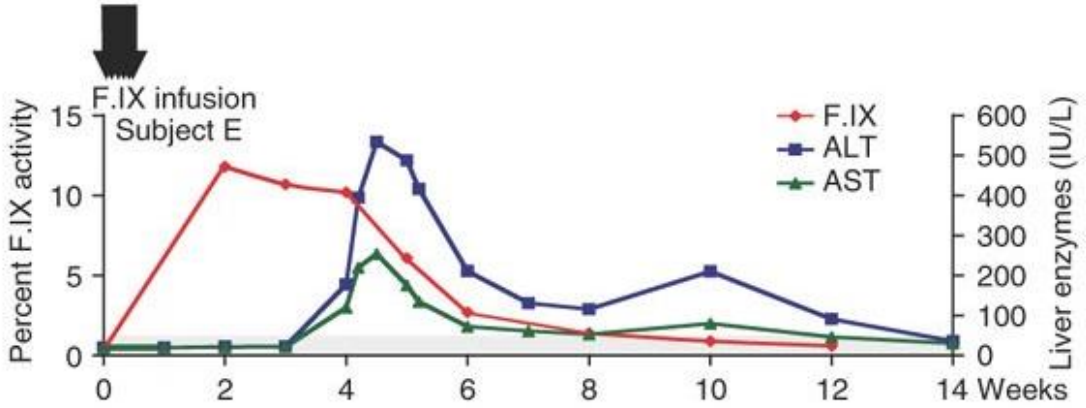
CrossMark

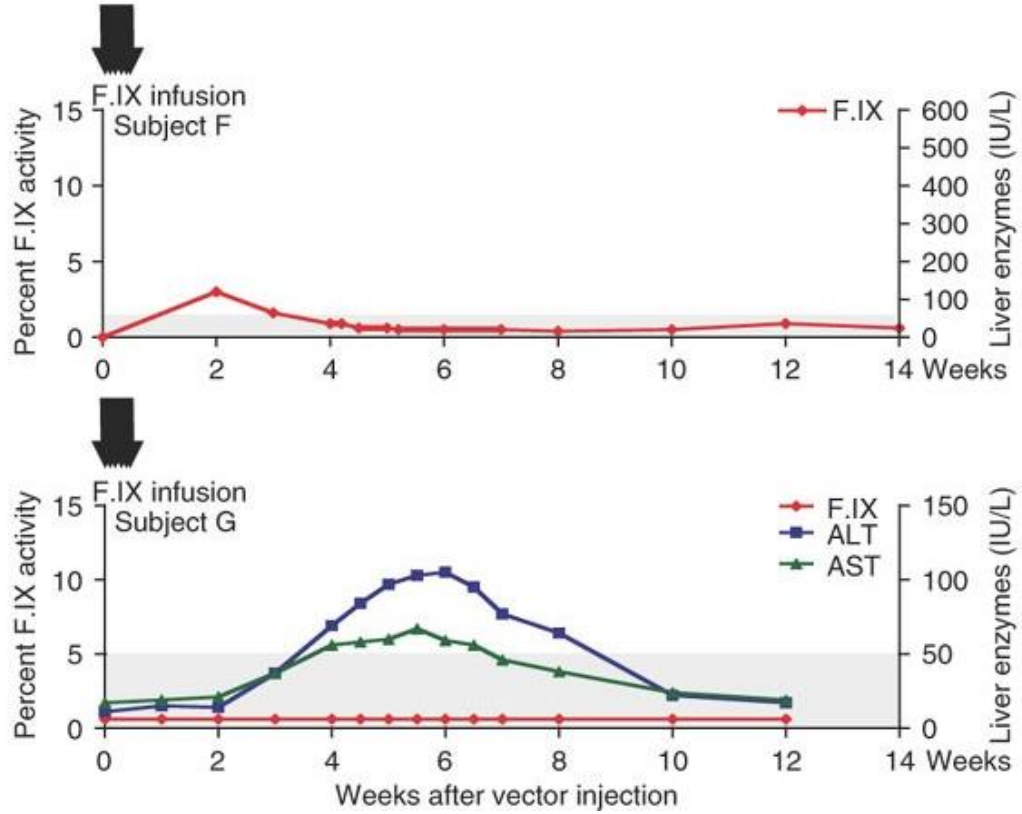
EASL JOURNAL OF HEPATOLOGY

EASL Clinical Practice Guidelines: Autoimmune hepatitis☆

European Association for the Study of the Liver*

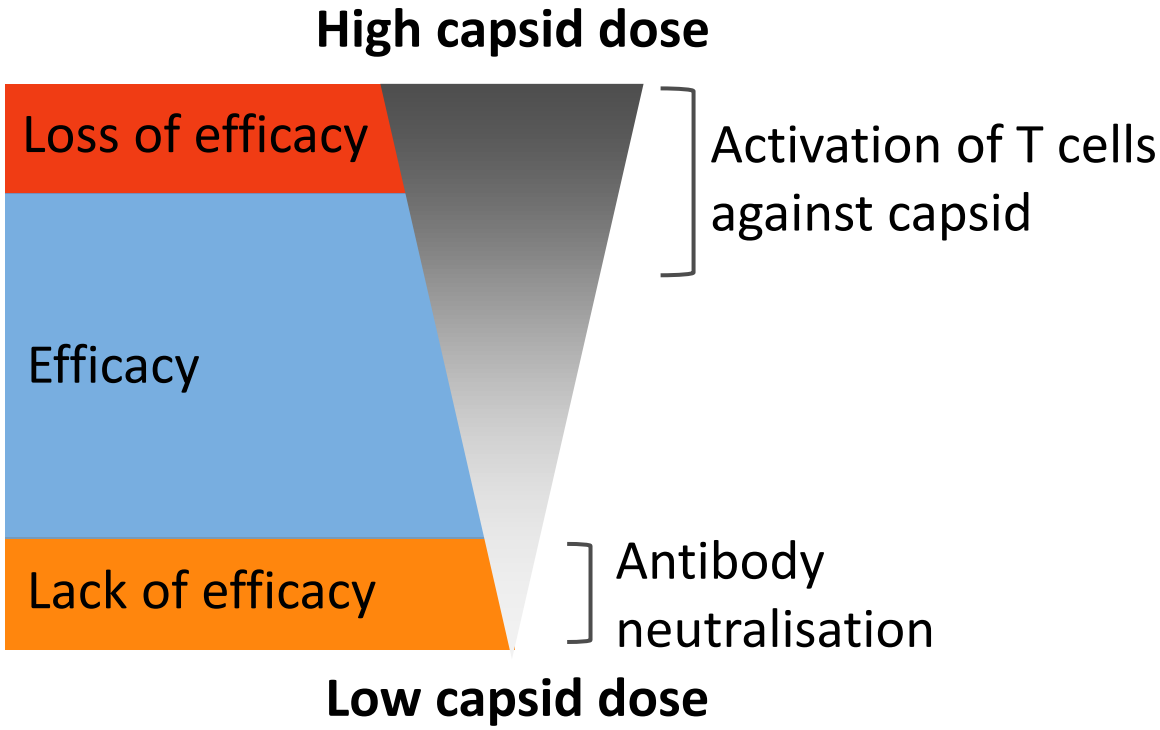
AAV gene therapy: vector-associated hepatitis





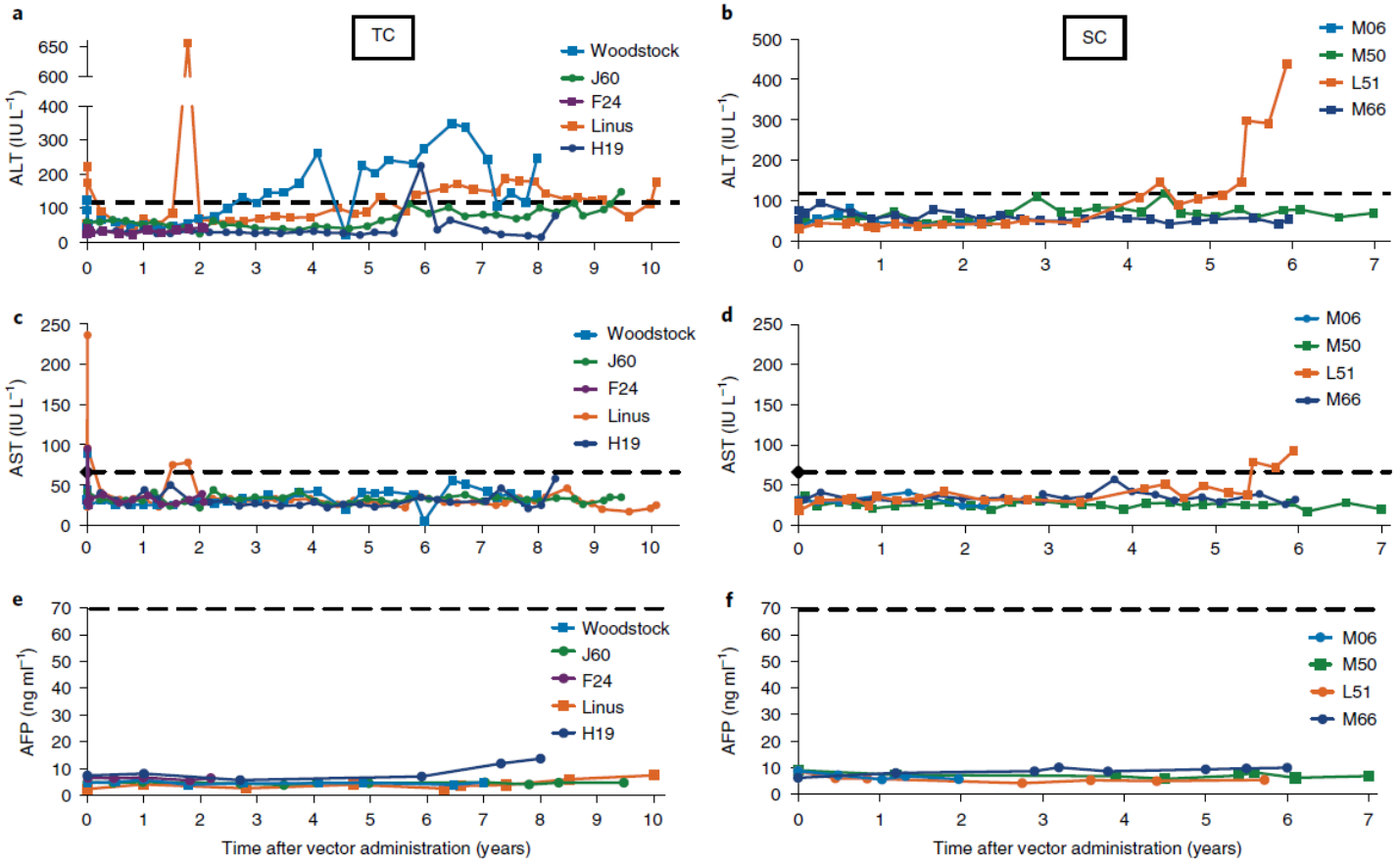
AAV gene therapy: vector-associated hepatitis

- Treatment with corticosteroids can control acute hepatitis[1] (usually 4–16 weeks)
- Lower vector doses – lower immunity against hepatocytes expressing vector antigens?[1–3]



How can vector doses be reduced while maintaining optimal transgene expression levels?[3]

Low frequency of elevated liver enzymes in dogs with haemophilia A treated with AAV gene therapy



AAV-based Gene Therapy of the Liver

Acute toxicity

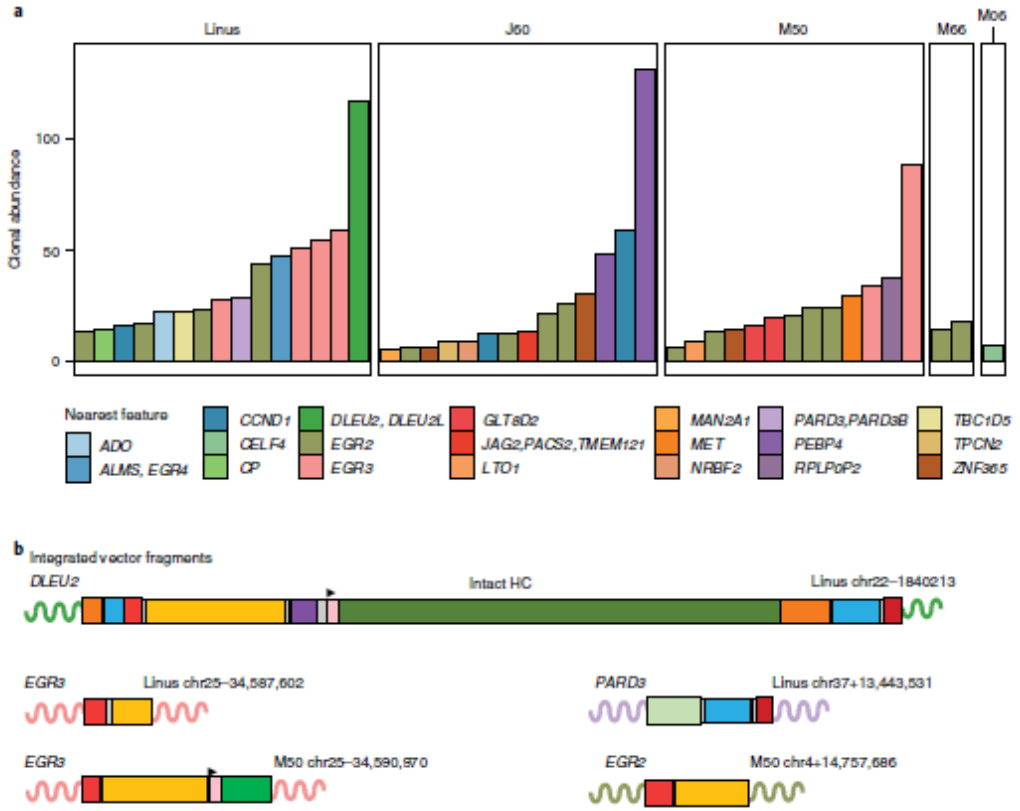
Long-term safety

comorbidities

Risk of hepatocyte clonal expansion?

A long-term study of AAV gene therapy in dogs with hemophilia A identifies clonal expansions of transduced liver cells

Giang N. Nguyen[1,8], John K. Everett[2,8], Samita Kafle[1], Aoife M. Roche[2], Hayley E. Raymond[2], Jacob Leiby[2], Christian Wood[1], Charles-Antoine Assenmacher[3], Elizabeth P. Merricks[4,5], C. Tyler Long[4,5], Haig H. Kazazian[6], Timothy C. Nichols[4,5], Frederic D. Bushman[2] and Denise E. Sabatino[1,7]



AAV-based Gene Therapy of the Liver

Acute toxicity

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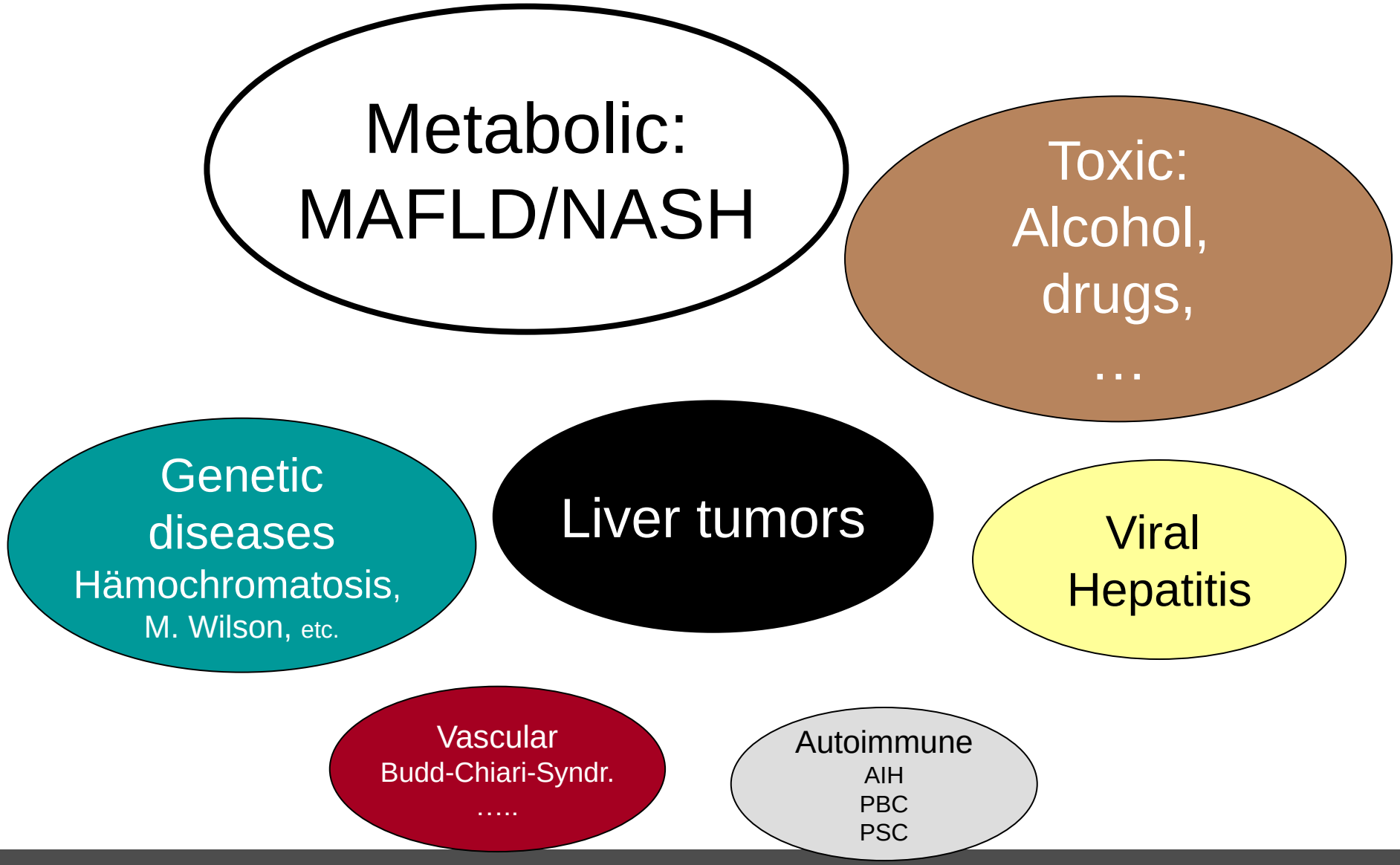
comorbidities

Comorbidities

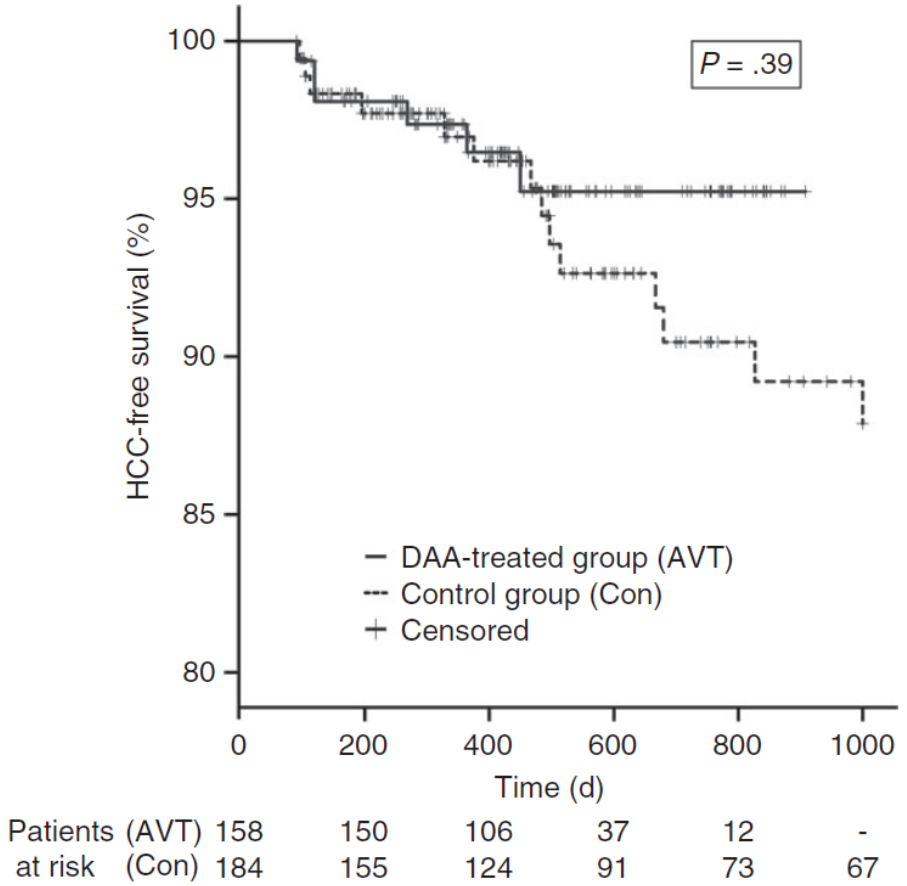


After Cure of HCV

Game is not over

Ongoing or Past HCV infection increases the risk of HCC

Population Groups	Incidence of HCC
Cirrhotic HBV carriers	3%-8%/year
HCV cirrhosis	3%-5%/year
Stage 4 primary biliary cirrhosis	3%-5%/year
Genetic hemochromatosis and cirrhosis	Unknown but probably >1.5%/year
Other cirrhosis	Unknown
Male Asian HBV carriers older than 40 years	0.4%-0.6%/year
Female Asian HBV carriers older than 50 years	0.3%-0.6%/year
HBV carriers with a family history of HCC	Higher than incidence without a family history
African/North American blacks with HBV	HCC occurs at a younger age.



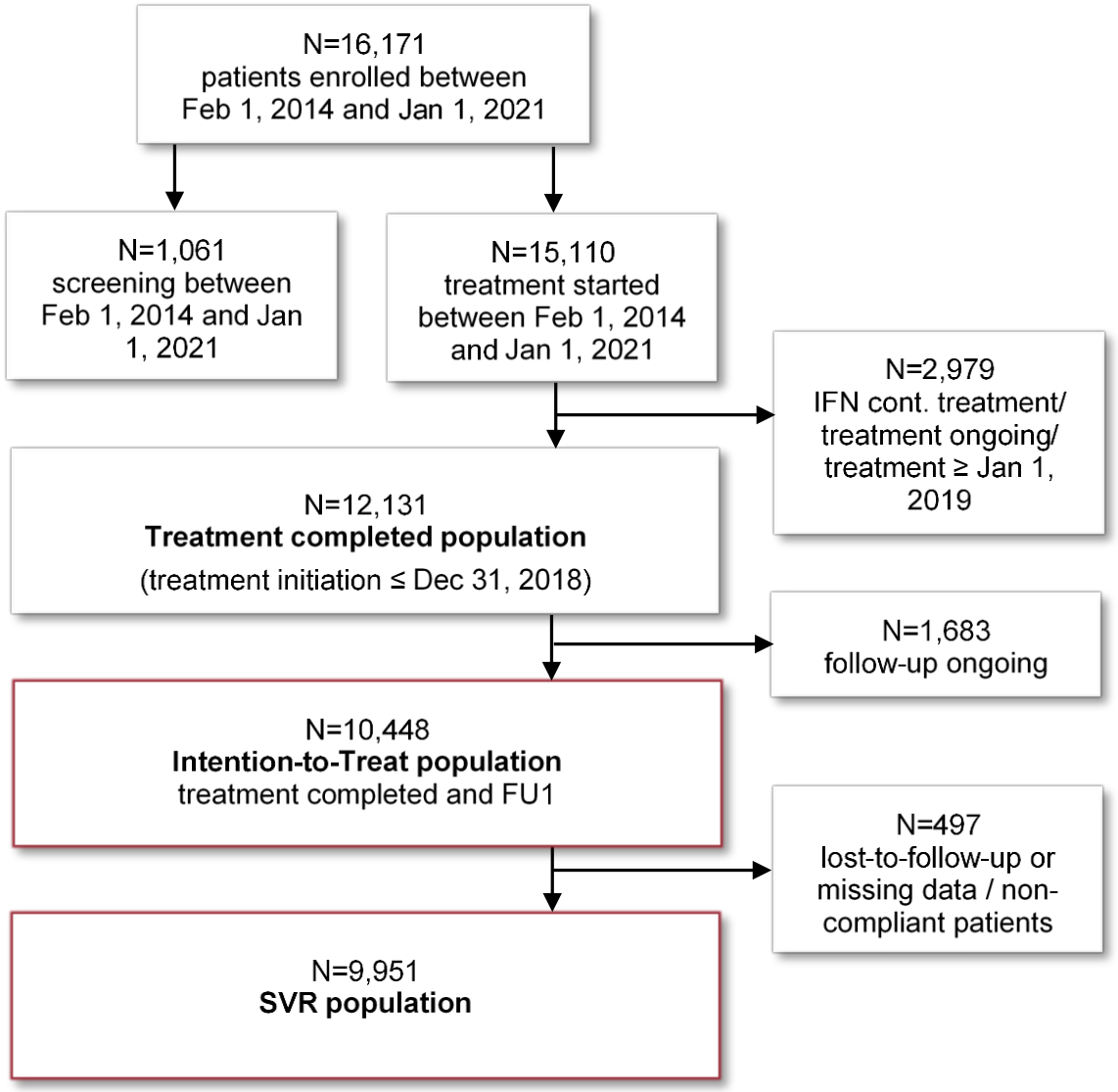
HCC-free survival in patients treated for HCV

HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; HCV: Hepatis C virus.
Left-hand table from: Herbst DA, Reddy KR. Clin Liver Dis 2012;1(6):180–2.
Right-hand figure from: Mettke F, et al. *Aliment Pharmacol Ther* 2018;47(4):516–25.

Persistent long-term risk of liver related complications in HCV patients after antiviral therapy - Data from the German Hepatitis C-Registry (EASL-ILC June 2021)

Heiner Wedemeyer, Peter Buggisch, Stefan Mauss, Albrecht Stoehr, Hartwig Klinker, Klaus HW Boeker, Gerlinde Teuber, Yvonne Serfert, Markus Cornberg, Heinz Hartmann, Dietrich Hüppe, Christoph Sarrazin, Karl-Georg Simon, Stefan Zeuzem, Thomas Berg, German Hepatitis C-Registry

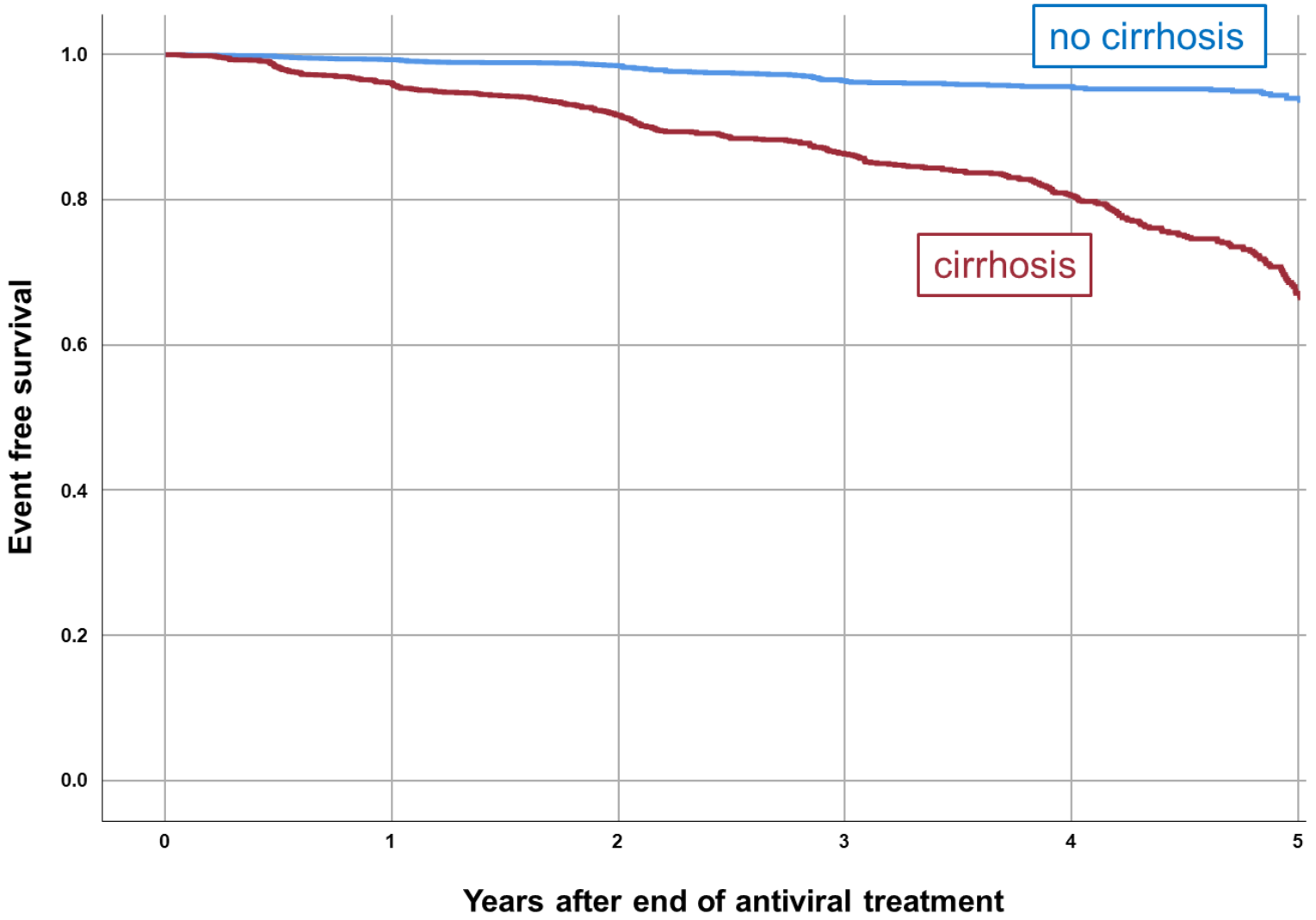
Patient flow



Prospective, multi-center, non-interventional study (data base extract Jan 1, 2021)

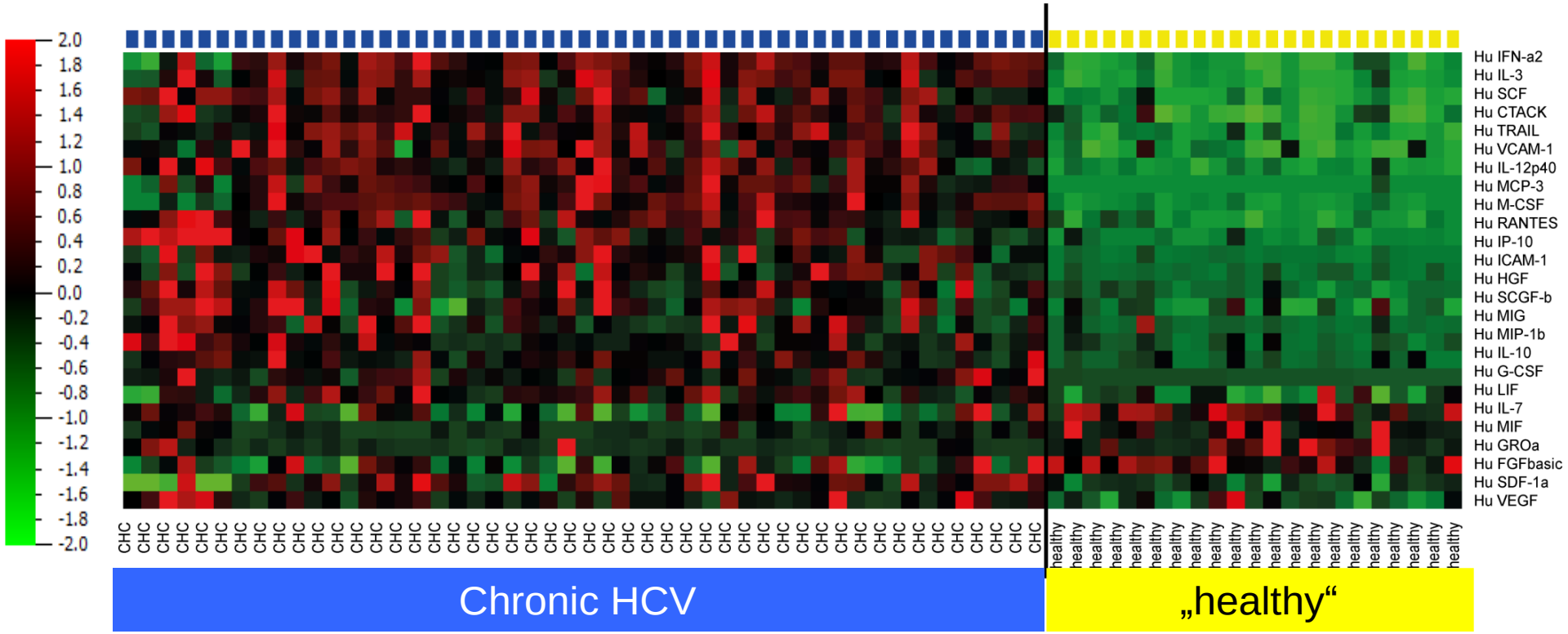
Results

- 33% (3,339/10,448) of patients had liver cirrhosis at BL
- 26% (2,712/10,448) were followed up for ≥3 years after EOT
- Antiviral treatment: +RBV: 2,359 patients, -RBV: 8,089 patients
- Overall SVR rates: ITT: 95% (9,951/10,448); Per protocol: 97% (9,824/10,157)
- Overall annual incidence of de novo HCC was 0.3% (SVR ITT patients)
- Annual post-treatment HCC risk in SVR ITT patients with liver cirrhosis
  - Years 1−2: 0.9%
  - Years 3−5: 0.5%



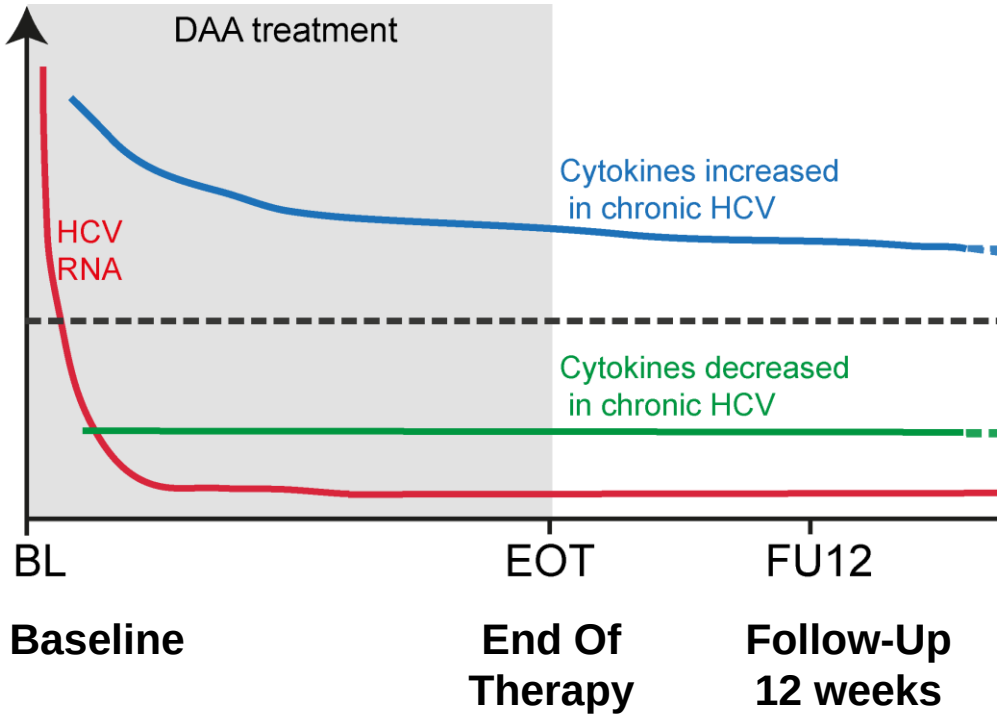
Kaplan-Meier curve analysis of liver related endpoint free survival of SVR patients with and without baseline liver cirrhosis during long-term follow up

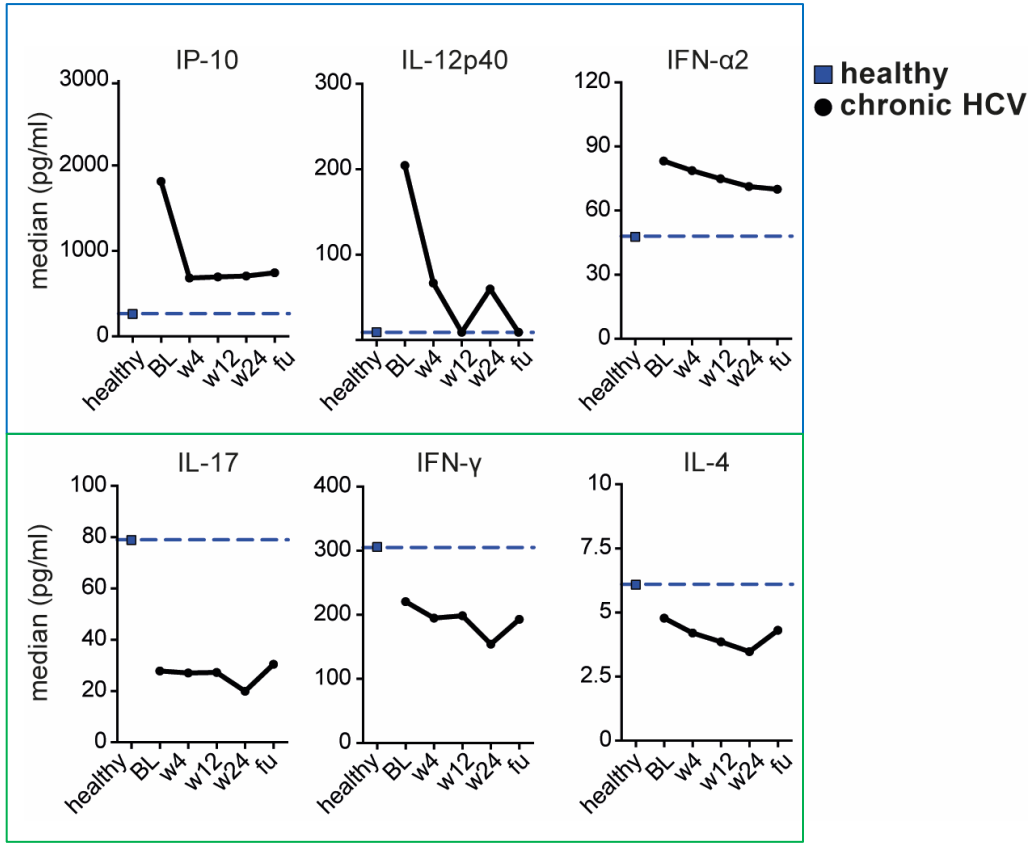
HCV induces an IFN response within the infected cell and is rather sensitive against the antiviral state triggered by IFNs, yet in most cases HCV persists (Metz et al., J Hepatol. 2013 Dec;59(6):1331-41.)



Owusu Sekyere S et al., Front Immunol. 2015 Jun 10;6:270.

HCV cure does not completely restore the altered cytokine and chemokine milieu 12-24 weeks after therapy compared to healthy controls





Hengst J et al., J Infect Dis. 2016 Dec 15;214(12):1965-1974.

„Long-HepC“?

J Infect Dis. 2016 Dec 15;214(12):1965-1974. doi: 10.1093/infdis/jiw457. Epub 2016 Sep 28.

Direct-Acting Antiviral-Induced Hepatitis C Virus Clearance Does Not Completely Restore the Altered Cytokine and Chemokine Milieu in Patients With Chronic Hepatitis C

Julia Hengst [1], Christine Susanne Falk [2 3 4], Verena Schlaphoff [1], Katja Deterding [1], Michael Peter Manns [1 3 4], Markus Cornberg [1 4], Heiner Wedemeyer [1 2 3]

J Infect Dis. 2021 Jan 31;jiab048. doi: 10.1093/infdis/jiab048. Online ahead of print.

Long-lasting Imprint in the Soluble Inflammatory Milieu despite Early Treatment of Acute Symptomatic Hepatitis C

Tanvi Khera [1 2], Yanqin Du [1], Daniel Todt [3 4], Katja Deterding [1 2], Benedikt Strunz [5], Svenja Hardtke [2], Amare Aregay [2], Kerstin Port [2], Matthias Hardtke-Wolenski [1 2], Eike Steinmann [3], Niklas K Björkström [5], Michael P Manns [2 6], Julia Hengst [2], Markus Cornberg [2 6 7], Heiner Wedemeyer [1 2 6], HepNet Acute HCV IV Study Group

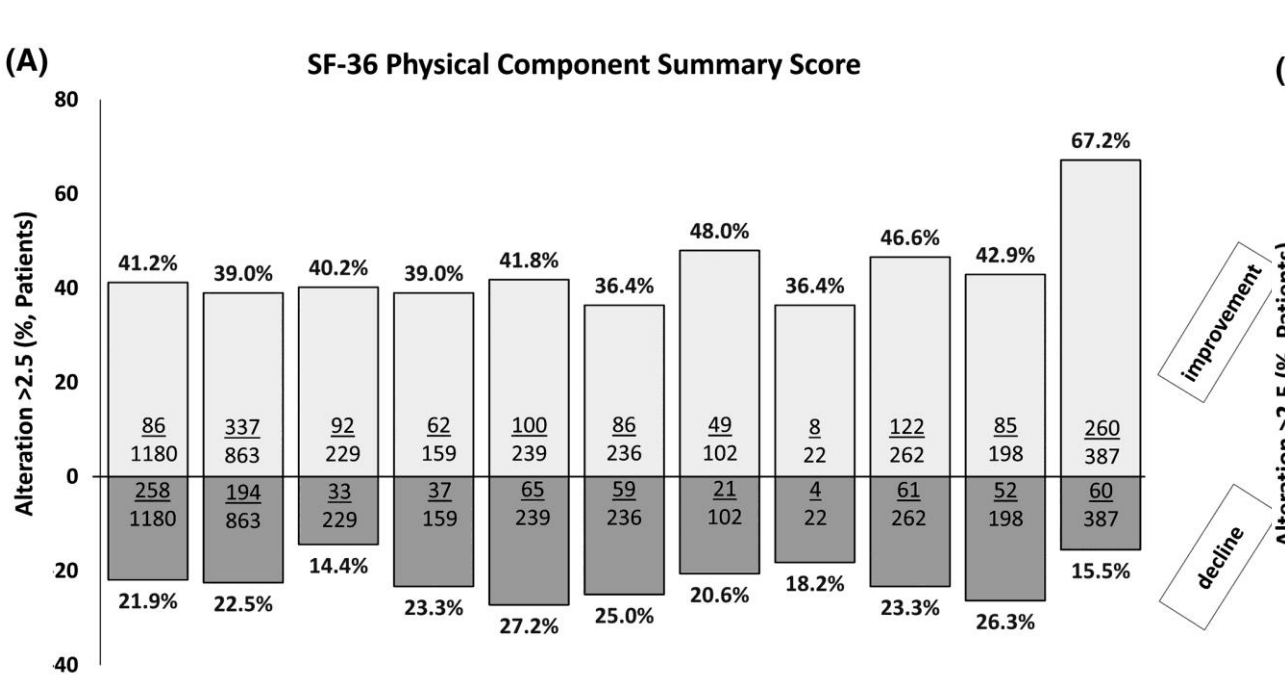
+ MAIT Cells: Hengst et al., EJI 2016
+ NK Cells: Strunz et al., Nat Comm 2018
+ gd T cells: Ravens et al., Front Immunol 2018
+ HCV-specific T cells, Aregay et al., J Hepatol 2019
+ post-liver transplantation, Aregay et al., Liver Transplantatiop 2021

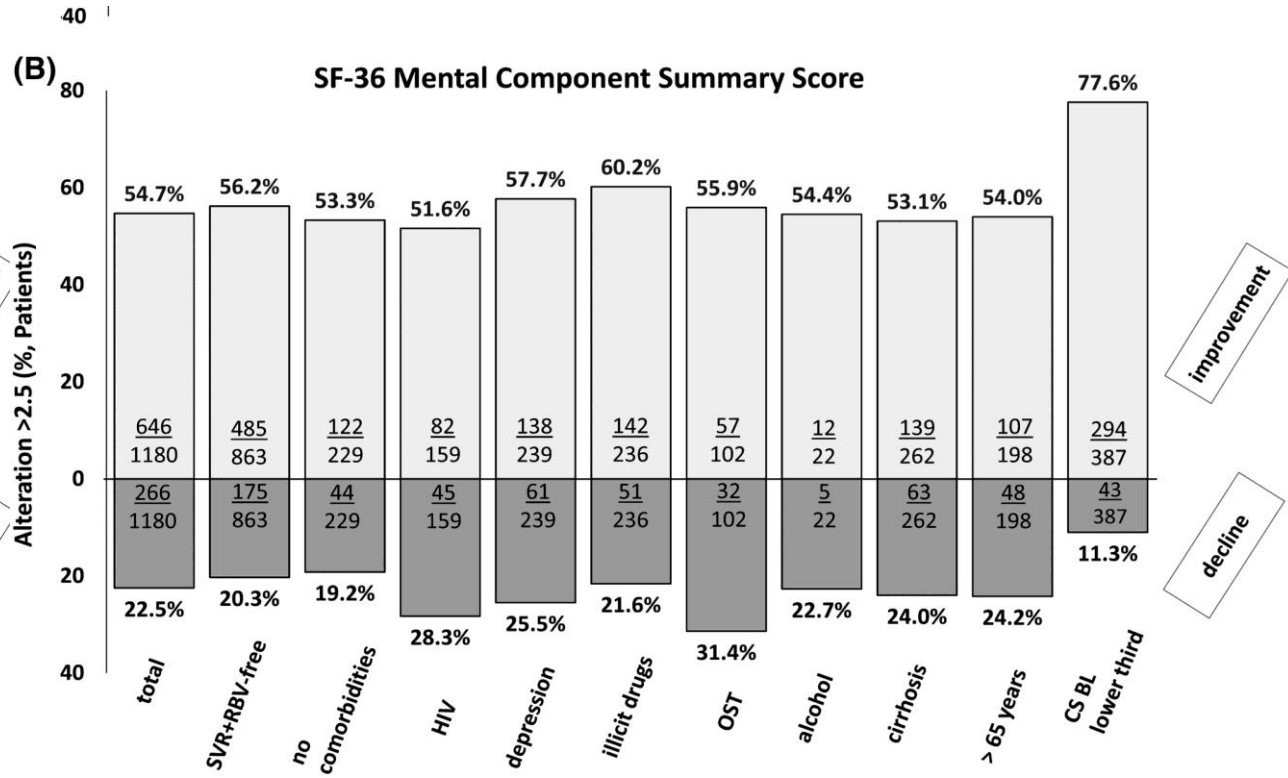
J Viral Hepat. 2021 May 18. doi: 10.1111/jvh.13546. Online ahead of print.

Only partial improvement in health-related quality of life after treatment of chronic hepatitis C virus infection with direct acting antivirals in a real-world setting- results from the German Hepatitis C-Registry (DHC-R)

Valerie Ohlendorf [1], Arne Schäfer [2], Stefan Christensen [3], Renate Heyne [4], Uwe Naumann [5], Ralph Link [6], Christoph Herold [7], Willibold Schiffelholz [8], Rainer Günther [9], Markus Cornberg [1], Yvonne Serfert [10], Benjamin Maasoumy [1], Heiner Wedemeyer [1 10], Michael R Kraus [11]

Not all patients improve QoL after HCV cure!

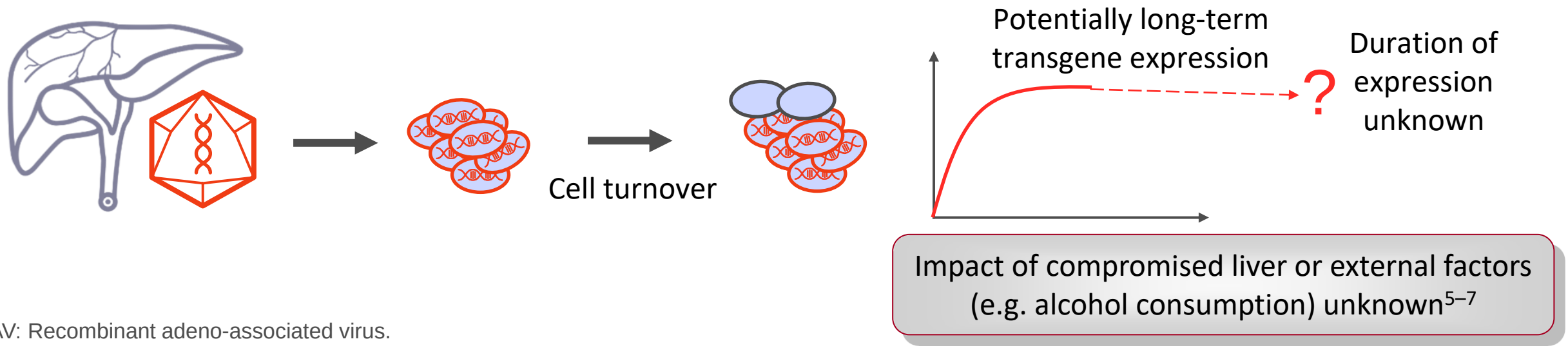





Deutsche
Leberstiftung

Impact of hepatocyte turnover on durability

- Predominantly **non-integrating** nature of rAAV may result in dilution of transgenes over time as cells undergo replication[1]
  - Human liver approximately **doubles** in weight at **4 months**, **16 months** and **6 years**, and by almost half again by 12 years[2]
  - Average life span of **adult hepatocytes** ranges from **200–300 days**[3,4]



rAAV: Recombinant adeno-associated virus.

Figure created using information from: Kattenhorn LM, et al. *Hum Gene Ther* 2016;27(12):947–61.
1. Colella P, et al. *Mol Ther Methods Clin Dev* 2017;8:87–104. 2. Coppoletta JM, Wolbach SB. *Am J Pathol* 1933;9:55–70. 3. Duncan AW, et al. *Gastroenterology* 2009;137(2):466–810. 4. Kattenhorn LM, et al. *Hum Gene Ther* 2016;27(12):947–61. 5. Maher JJ. *Alcohol Res Med World* 1997;21:5–12. 6. Sidonio RF, et al. *Blood Rev* 2020;100759. 7. George LA. *Hematology Am Soc Hematol Educ Program* 2017;587–94.

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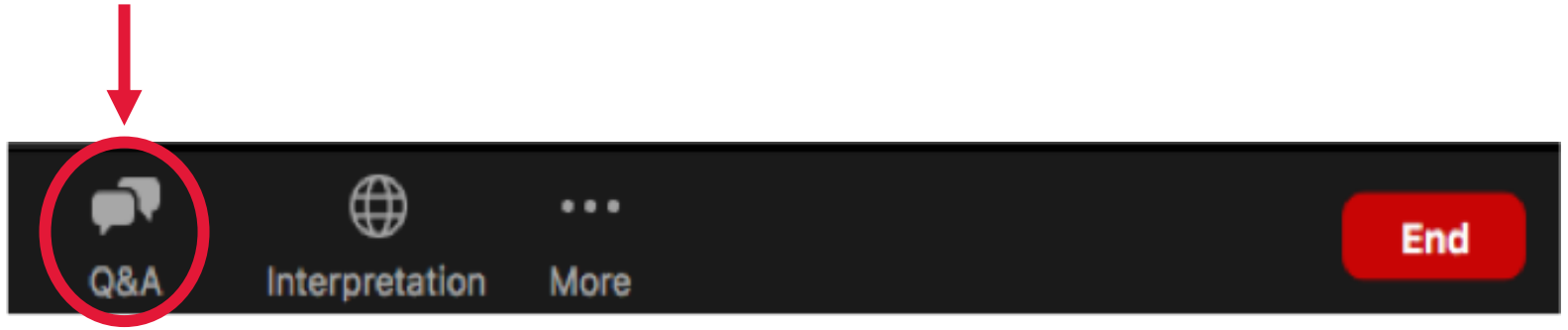
QUESTION & ANSWER

Please submit your questions in the Q&A box



SPEAKERS

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U.S.A.

Dawn Rotellini
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Updates in von Willebrand Disease from the ISTH 2021 Virtual Congress

Nathan T. Connell, MD, MPH
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Harvard Medical School
Boston, Massachusetts, USA

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Speaker disclosures

Shareholder	None
Grant / Research Support	None
Consultant	None
Employee	Brigham and Women's Hospital
Paid Instructor	None
Speaker bureau	None
Other	Non

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Von Willebrand Disease

- The most common inherited bleeding disorder
- Inherited by men and women equally, but disproportionately affects women due to heavy menstrual bleeding and postpartum hemorrhage
- The International Society on Thrombosis and Haemostasis holds an annual Congress for presentation of basic, translational, and clinical science.
- The ISTH Scientific and Standardization Committee (SSC) has a subcommittee on VWF

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VWD Topics from the ISTH

- Updates from the VWF SSC
- Key Clinical Science Updates in von Willebrand Disease

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VWF SSC

- VWD Guidelines: Clarity and Controversy (Makris)

- Discussion about the diagnostic thresholds, the treatment options, and the applicability to global populations

ASH ISTH NHF WFH Guidelines on the Diagnosis and Management of VWD
www.wfh.org/VWDGuidelines

Links to the guidelines (open access, freely available)
Patient resources about the guidelines
Links to collaborator resources

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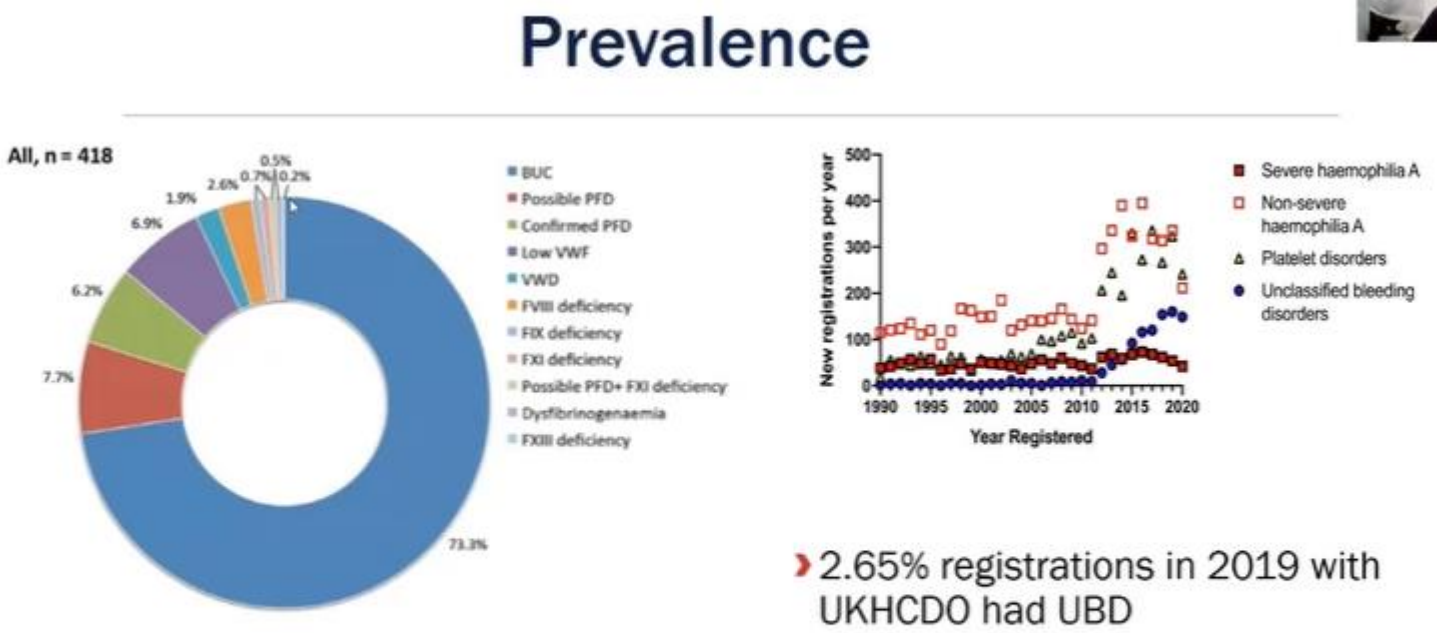
VWF SSC

- Beyond VWD: Bleeding of Unknown Cause (Thomas)



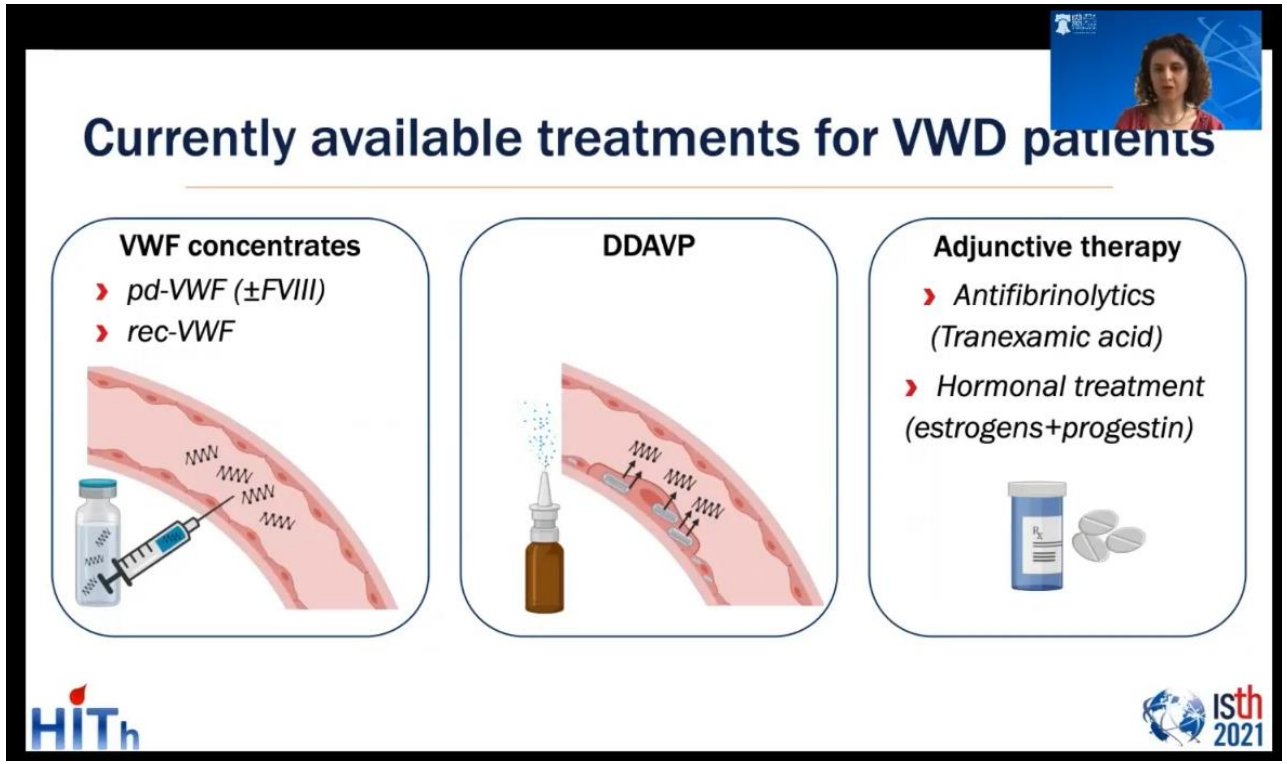
Think about:
Collagen Vascular Disorders
Platelet Function Defects
Tissue factor pathway inhibitor

Desmopressin +/- TXA often effective in patients with BUC

Gebhart *et al*, *Haemophilia*, 2018; data courtesy of the UKHCDO (unpublished) and figure courtesy of Mike Desborough

VWF SSC

- New Treatment Options for VWD (Casari)



Genetic therapies being investigated include siRNA based effects, which may only have mild effect on VWD phenotypes, and gene-editing techniques that would be particularly helpful in patients with double-negative *VWF* mutations

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VWF SSC

- Pathogenesis of Microthrombi in SARS-CoV2 Infection: Role of Von Willebrand Factor and ADAMTS-13 (Dupont)
- Collaborative Study of the WHO VWF Concentrate (Thelwell)
- Towards a Unifying Activation Mechanism of VWD (Li)
- ADAMTS13 Auto-Antibody Binding (Vanhoorelbeke)

VWF SSC

- Project Update: Von Willebrand Factor Nomenclature (Haberichter)

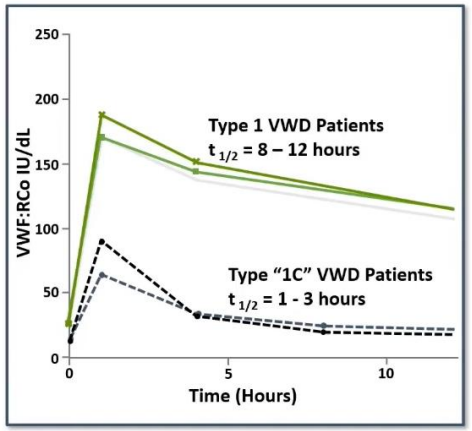
Quantitative

- Type 1: Partial deficiency of VWF
- Type 3: Virtually complete VWF deficiency

Qualitative (loss of function)

- Type 2A: loss of HMW multimers
- Type 2B: gain-of-function platelet binding (with loss of HMW multimers)
- Type 2N: Defect in binding FVIII
- Type 2M: Defect in VWF binding to platelets or collagen

Type 1 VWD With Reduced VWF Survival



DDAVP may be ineffective for treatment of major bleeding in subjects with a Reduced VWF Survival phenotype

Type 1C will be an officially accepted VWD subtype

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VWD Clinical Abstracts

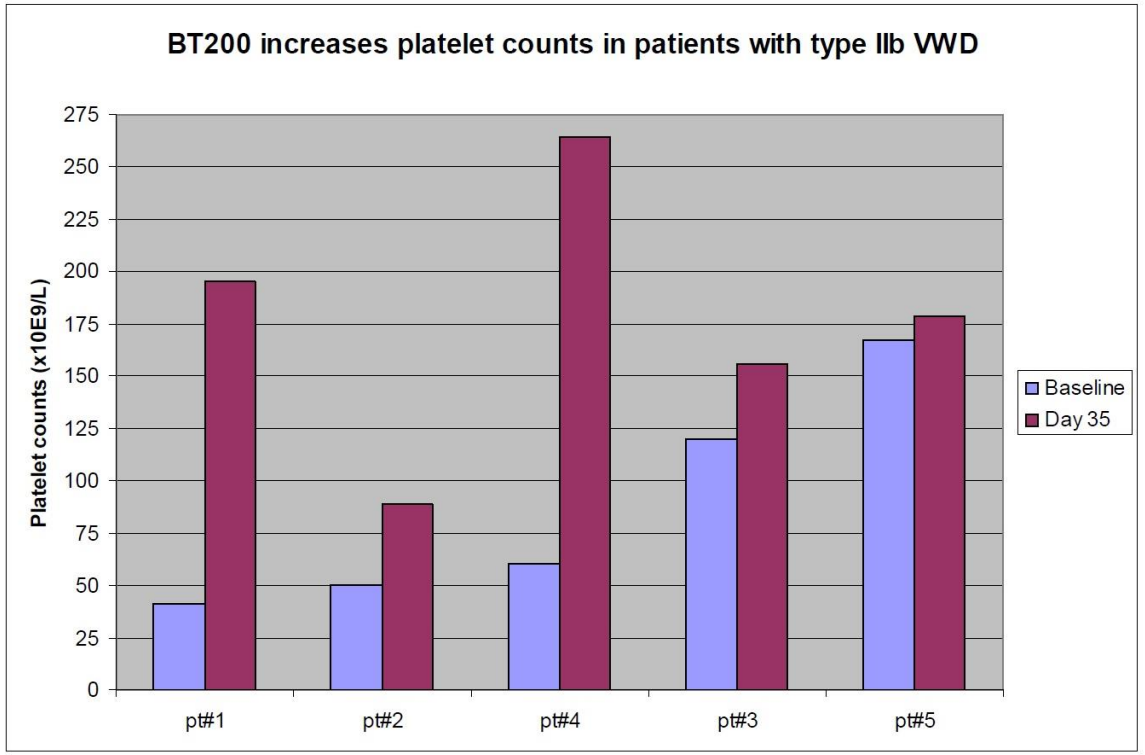
OC 13.2 Response to treatment for gastro-intestinal bleeding in patients affected by Von Willebrand disease (Biguzzi)

- GI Bleeding is common in VWD, especially with certain subtypes. At one center in Milan (16% lifetime incidence)
- VWF has effects on VEGF → angiodysplasia
- 19% of patients with GI bleeding needed long-term prophylaxis or rescue therapy (surgery, octreotide, lanalidomide etc.)

VWD Clinical Abstracts

OC 72.1 BT200 Increases von Willebrand Factor (VWF), FVIII and Platelet Counts in Patients with von Willebrand Disease (VWD) Type Iib (Ay)

- BT200 is a pegylated aptamer binding A1 domain of VWF, enhancing VWF/FVIII levels by decreasing clearance
- BT200 3 mg on study days 1,4,7, followed by 6 mg weekly



Patients ordered according to platelet counts at baseline

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VWD Clinical Abstracts

PB0923 Clinical, Economic, and Quality of Life Burden Associated with von Willebrand Disease (VWD) in Adults and Children: Systematic and Targeted Literature Reviews (Castaman)

- 25 cost and resource use studies (79,885 patients of all ages with VWD), costs varied widely;

- Higher costs for patients with VWD compared to patients with non-VWD disorders were reported.

- In 17 HRQoL studies (5,730 patients of all ages with VWD), all studies assessing treatment impact on VWD (except one) reported an improvement in single or multiple components of HRQoL scales.

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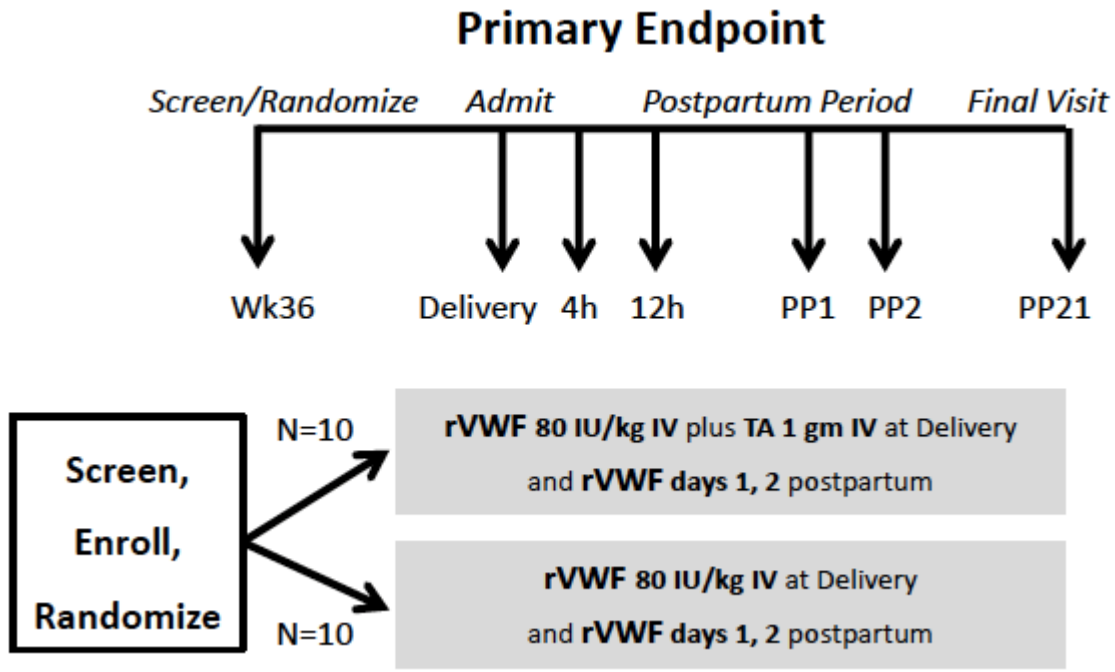
VWD Clinical Abstracts

PB0944 The von Willebrand Disease-Woman (VWD-Woman) Trial: A Pilot Study Comparing Recombinant von Willebrand Factor (rVWF) plus Tranexamic Acid (TA) vs. rVWF Alone in the Prevention of Postpartum Hemorrhage in Women with von Willebrand Disease



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VWD State of the Art: RPTH

Pregnancy, postpartum and periods: Current challenges in the management of women with Von Willebrand disease

Michelle Lavin MB, PhD, FRCPath

Challenges in the management of women with VWD

Periods

Identifying & testing women with HMB

Objective measurement of menstrual loss

Best first-line therapies for women with VWD

Pregnancy

Understanding pregnancy induced plasma VWF increase

Optimal plasma VWF target for delivery

Consistent approaches to neuraxial anaesthesia

Postpartum

Secondary postpartum haemorhage: Definition, prevention and early identification

Iron status in the postpartum

Future pregnancy planning

Res Pract Thromb Haemost. 2021;5:e12532.
https://doi.org/10.1002/rth2.12532

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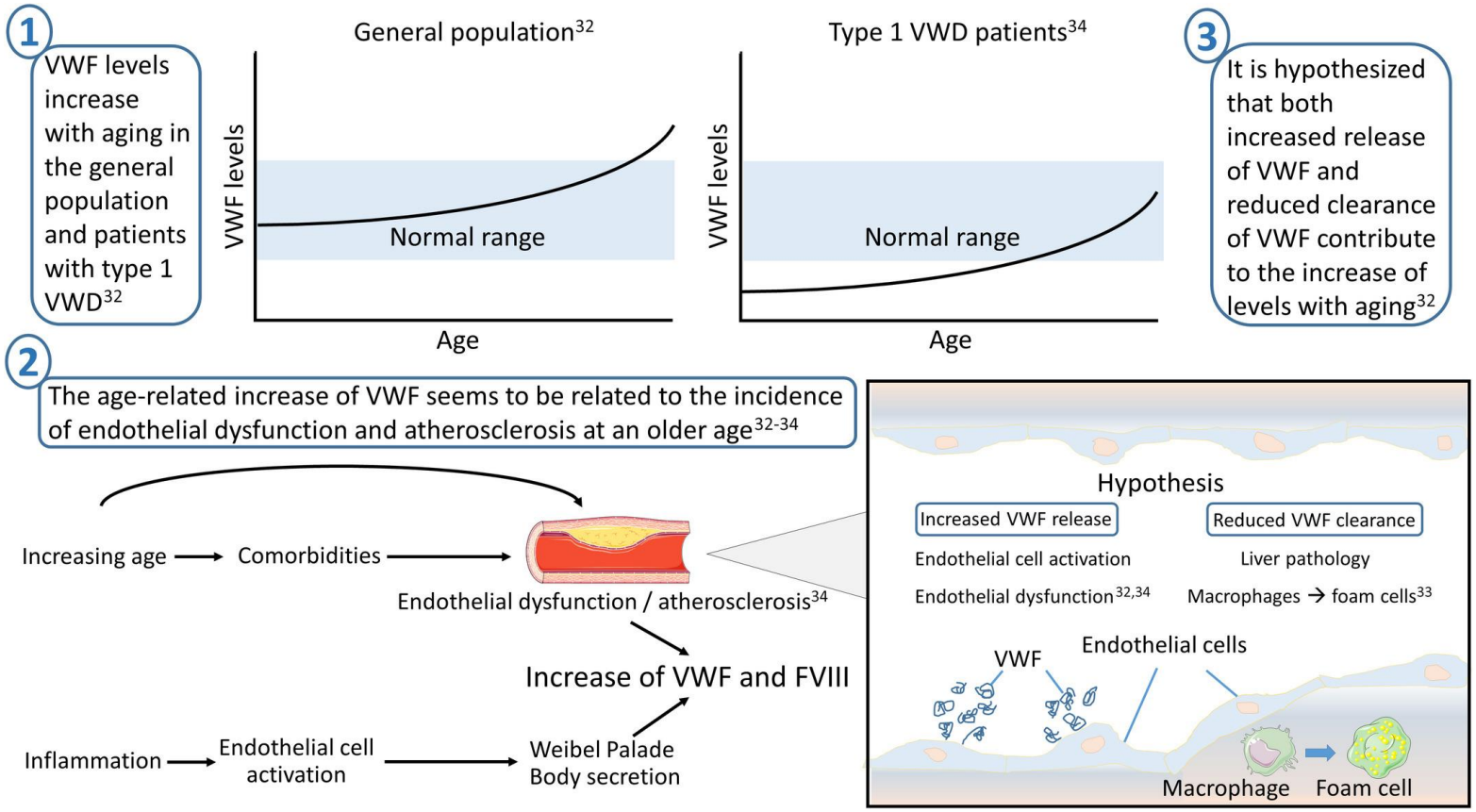
VWD State of the Art: RPTH

The impact of aging and inflammation on plasma Von Willebrand factor levels
Frank W.G. Leebeek



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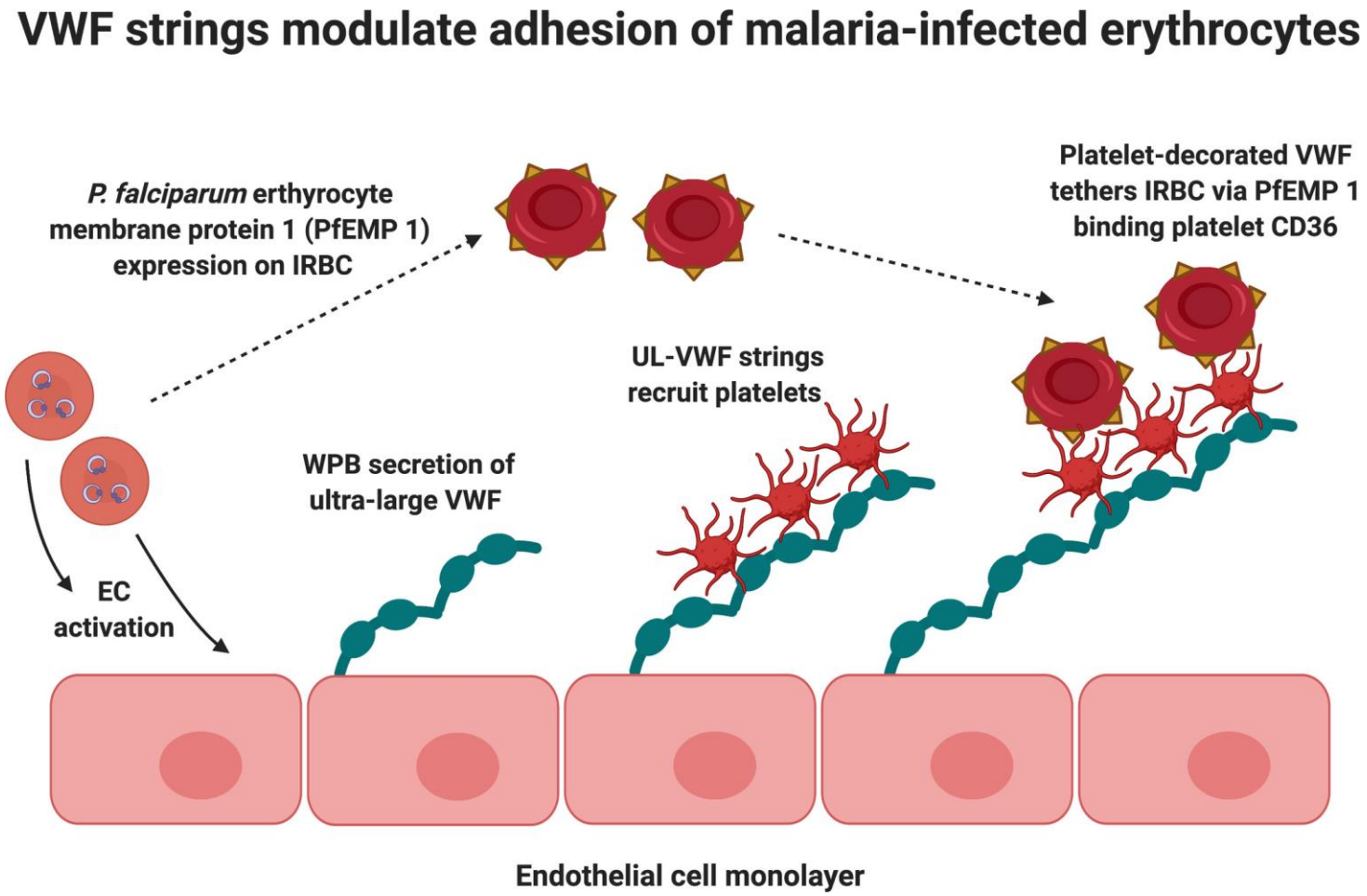
VWD State of the Art: RPTH

Von Willebrand factor modulates adhesion of malaria-infected erythrocytes to endothelial cells
James S. O' Donnell



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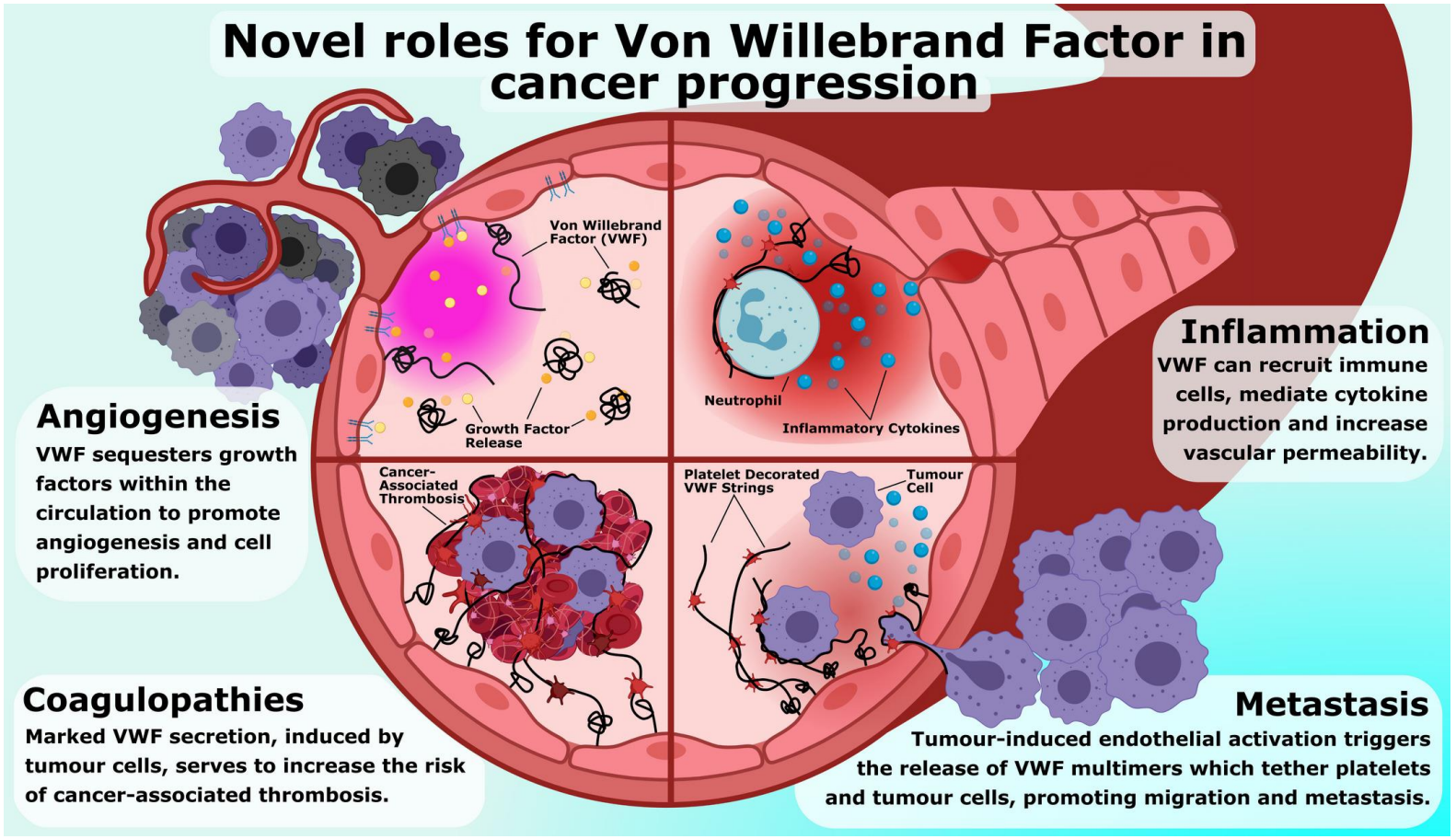
VWD State of the Art: RPTH

Von Willebrand Factor structure-function in the regulation of cancer metastasis
Jamie O'Sullivan



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WFH Global Summit on Women & Girls with Bleeding Disorders

Dawn Rotellini
WFH Board Member
Chair, WIBDs Committee

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Speaker disclosures

Shareholder	
Grant / Research Support	
Consultant	Bayer, BioMarin, Pfizer, Roche – all honoraria goes to the National Hemophilia Foundation
Employee	Officer, NHF
Paid Instructor	
Speaker bureau	
Other	

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- 1034 Registrants from 118 Countries
- 497 Attended Sessions from 82 Countries
- Top Ranked Sessions: Multidisciplinary Care for WGBDs, Importance of OB-GYNs in the Comprehensive Care Team, Oral Health: Have We Bitten Off More Than We Can Chew?

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WFH Global Summit on women & girls with bleeding disorders

July 8–10, 2021

This was a great conference. It was well-planned and organized. I found the balance between materials for providers and consumers one of the most effective elements of the sessions I attended. I learned so much and was definitely inspired.

I learned a lot. Outreach and Diagnosis - Michelle Lavin's presentation, Pamela Narayan and Christi Humphrey - both perspectives were good, Oral Health Hot Topics was GREAT

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Summit Format

Video Testimonials

Video Intros to Each Day

Plenaries

Education Sessions

Ask the Experts Sessions

Hot Topic Exchanges

Toolkit Sessions

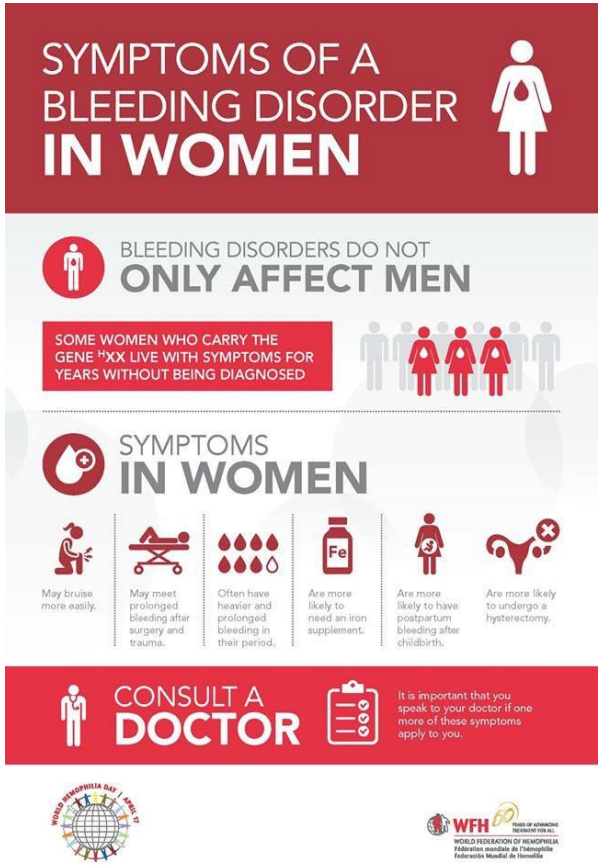
WFH Global Summit on
women & girls
with bleeding disorders July 8–10, 2021

Highlight of Sessions and Feedback

advocacy
to change "what is"
into "what should be"

Highlights: Plenary Sessions

- Multidisciplinary care for Women and Girls with Bleeding Disorders: What Does It Look Like?
- Outreach and Diagnosis
- Signs, Symptoms and Empowerment for WGBDs (Recognition and Speaking Up)
- What are the Health Outcomes in WGBD (Optimal Health Outcomes, Data and Why It Matters)



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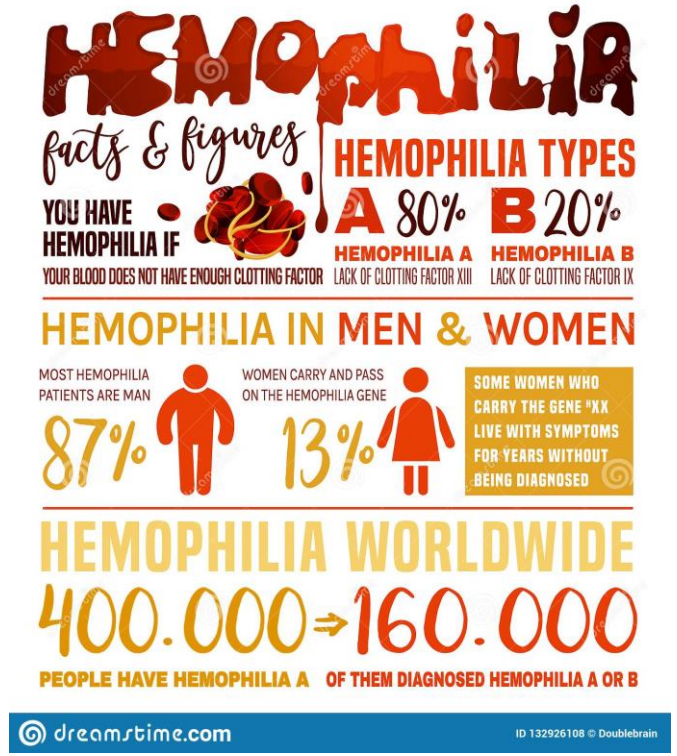
Highlights: Education Sessions

- WGBDs Experiences: Physiotherapist Perspective, Psychosocial Perspective, OBGYN Perspective
- Reproductive Choices for Women with Bleeding Disorders (OB-GYN, Genetic Counselors, Patient Perspective)
- Stages of Life: Preparing for Menarche, Reproductive Life, Preparing for Menopause and Aging Health Issues



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Highlights: Hot Topic Exchanges

- Importance of OB-GYNs in the Comprehensive Care Team
- Oral Health: Have We Bitten Off More Than We Can Chew
- Next Level Stigma on Girls, Women, Families: “Bleeding Through”
- Sexual Intimacy: Taboos Talking About Women with Bleeding Disorders & Sex
- Current and Future Product Portfolio: What Exists Today and What is Missing?

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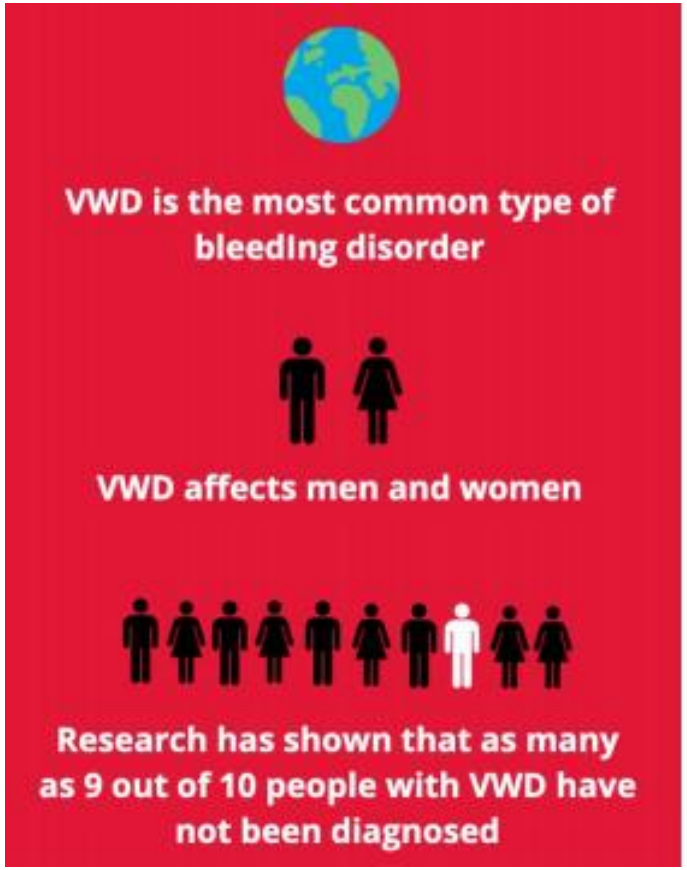
Highlights: Ask the Experts

- Heavy Menstrual Bleeding: When to Seek Treatment? (Getting Access to Treatment)
- WGBDs and Rare Bleeding Disorders/Platelet Disorders Awareness
- Heavy Menstrual Bleeding in VWD
- How will the 2021 International VWD Guidelines Improve Diagnosis, QOL, and General Health of Women Living with VWD



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Highlights: Toolkit Sessions

- Girls/Pre-adolescents: How to Talk About Periods (Preparation and Prevention)
- Speaking and Understanding Each Other's Languages (Patient and Providers) – Getting Your Voice Heard, Sharing Best Practices of Building, Understanding and Knowledge
- Action and Ways to Address the Disparities in Care, Treatment and Diagnosis: Using VWD and Hemophilia Guidelines, EAHAD Principles, and Global Initiatives for Advocacy

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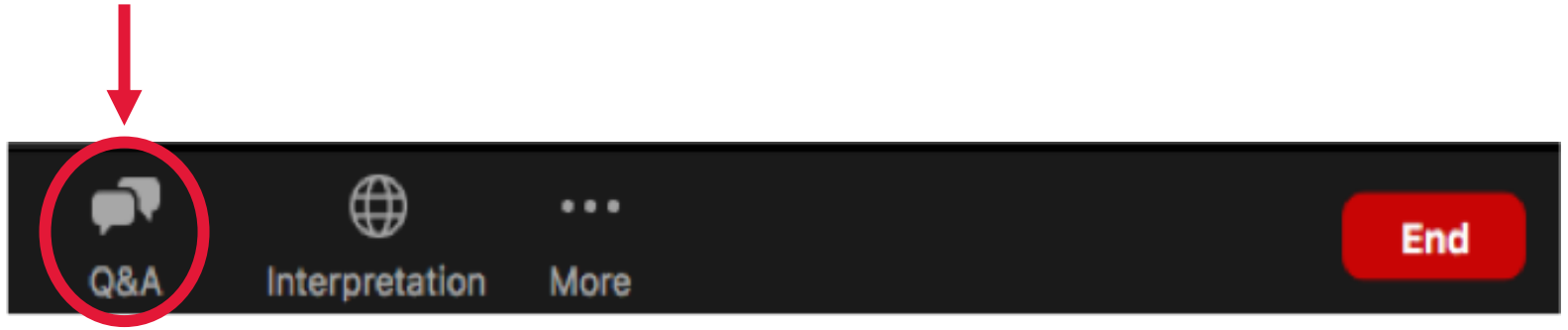
QUESTION & ANSWER

Please submit your questions in the Q&A box



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Prophylaxis with Limited Resources: Achievement and Expectations

Panel Discussion

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Prophylaxis in Hemophilia

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- Emna Gouider
- Kate Khair
- Manuel A. Baarslag (PWH)
- Lisa Bagley (PPWH)
- Francisco de Paula Careta (PWH)
- Rolf C. R. Ljung
- Margaret V. Ragni
- Elena Santagostino
- Glenn F. Pierce
- Alok Srivastava

72 | WILEY Haemophilia

Chapter 6: Prophylaxis in Hemophilia

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[12]Department of Haematology, Christian Medical College, Vellore, India

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PWH, person with hemophilia, PPWH, parent of person with hemophilia.

What is prophylaxis?

OLD	NEW
…the regular intravenous (IV) infusion of the missing clotting factor VIII (FVIII) in people with hemophilia A and factor IX (FIX) in people with hemophilia B, given in order to increase the FVIII/FIX level with the intent to prevent bleeding.[1]	The regular administration of a hemostatic agent/ agents with the goal of preventing bleeding in people with hemophilia while allowing them to lead active lives and achieve quality of life comparable to non-hemophilic individuals.[2]

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1. Blanchette VS, et al. Definitions in hemophilia: communication from the SSC of the ISTH. J Thromb Haemost. 2014;12(11):1935-1939.
2. Chapter 6: Prophylaxis in Hemophilia in Srivastava A et al. WFH Guidelines for the Management of Hemophilia, 3rd ed, Haemophilia, 2020.

Standard of care everywhere

Recommendation 6.2.1

For patients with severe phenotype hemophilia A or B, especially children, the **WFH recommends regular long-term prophylaxis as the standard of care** to prevent hemarthrosis and other spontaneous and breakthrough bleeding, maintain musculoskeletal health, and promote quality of life. When prophylaxis is not feasible, **episodic therapy** is essential treatment for acute hemorrhages, **but it will not prevent long-term joint damage**.

Recommendation 6.1.1 Remark

In countries with significant healthcare constraints, the **WFH still advocates for the use of prophylaxis** over episodic therapy but recognizes that **less intensive prophylaxis may be used**.

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Chapter 6: Prophylaxis in Hemophilia in Srivastava A et al. WFH Guidelines for the Management of Hemophilia, 3rd ed, Haemophilia, 2020.

Requirements for successful haemophilia prophylaxis

C. Hermans / Personal Views and Experience

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Prophylaxis with Limited Resources

Ampaiwan Chuansumrit, MD

International Hemophilia Training Center - Bangkok

Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

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Home Treatment for Hemophilia in Thailand

Improving outcome and decreasing hospitalization

- Early episodic treatment at home was initiated in 1979
- 1979-1982: 10 patient attended home treatment
- Mean age: 10 years old
- Frozen cryoprecipitate and later fresh dry plasma

Expanding home treatment to other patients and family

- Having blood products at home or shared refrigerator
- Preparing blood products or factor concentrates
- Practicing aseptic venipuncture process

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First Study of Low Dose Prophylaxis for Thai Hemophilia Patients in 1994

Pilot study proven – patient could be back to normal life

- Patient characteristics
  - 6 patients with hemophilia (median age 12 years old)
- Condition
  - Prophylactic treatment with factor VIII concentrates
- Dosing
  - 10-15 units per kg twice weekly for one year
- Results
  - Mean annual bleeding rate was reduced from 11.5 to 2.3
  - Absence from school was reduced, no need for hospitalization

Chuansumrit A, et al. Southeast Asian J Trop Med Public Health 1995;26:243-246.

Low-Dose Prophylaxis with Fixed-Dose 500 U FVIII Twice Weekly

Factor VIII Concentrate Produced by the National Blood Center, Thai Red Cross Society

- 50 patients with hemophilia A (severe 39, moderate 11)
- Mean age 20 years; mean weight 56 kg

Mean dose of factor VIII	9.6 units/kg
Patient with zero bleeds	24 patients (48%)
Patient with breakthrough bleeds: *60 spontaneous;* *5 trauma-related*	26 patients (52%)
1 episode	8 patients
2 episodes	8 patients
3 episodes	5 patients
4 episodes	2 patients
6 episodes	3 patients

- **No patient required hospitalization**
- **Patient with target joints exhibited more bleeding episodes compared with those without (63% vs 33%; p<0.05)**

Chuansumrit A, Sosothikul D, Natesirinilkul R, et al. Haemophilia 2018;24:e387-e390.

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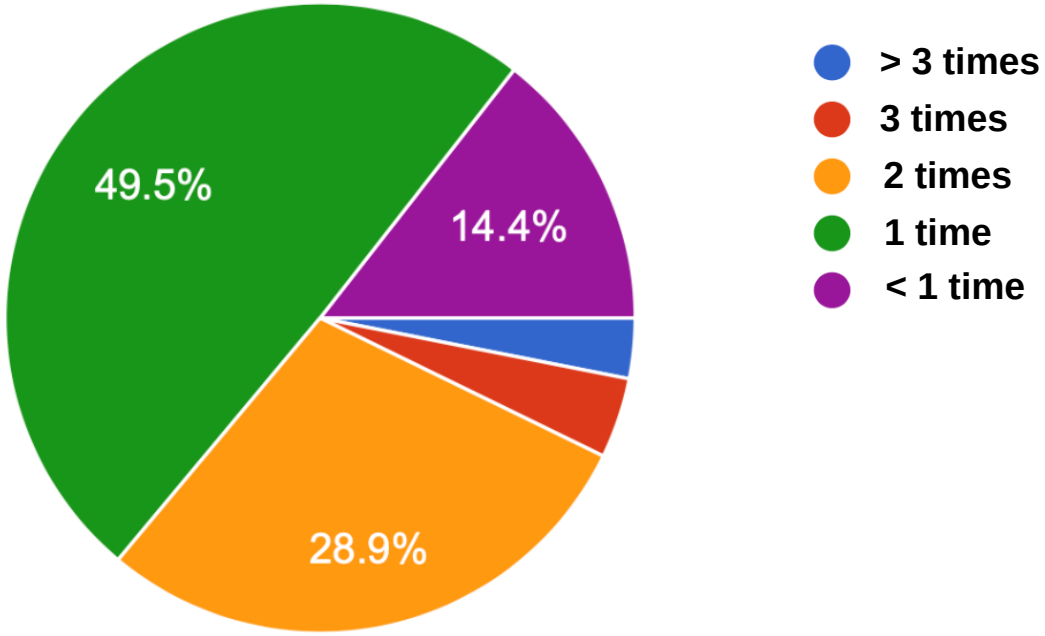
Thai Adult Patients with Hemophilia

How many injection per week?
97 responses



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Prophylaxis in Senegal

Saliou Diop, MD, MSc
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WFH board member

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Speaker disclosures

Shareholder	None
Grant / Research Support	None
Consultant	None
Employee	Université Cheikh Anta Diop Dakar Senegal
Paid Instructor	None
Speaker bureau	Novo Nordisk, Novartis, Octapharma
Other	None

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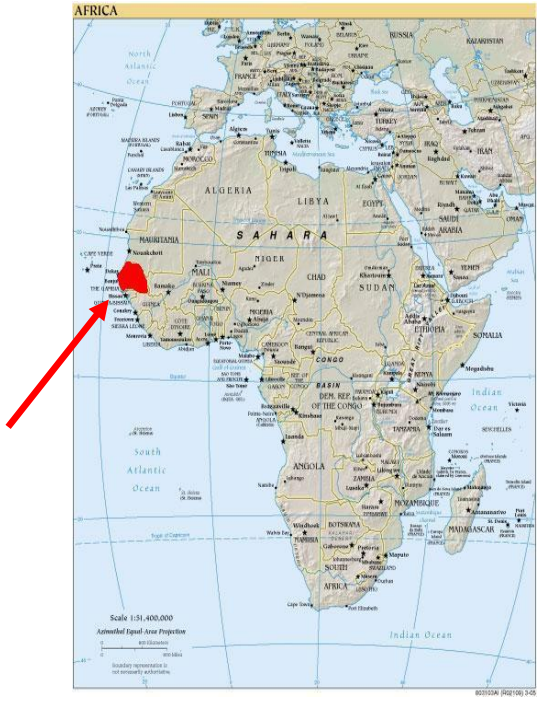
Senegal



- Population: 16,526,037 (2020)
- No of hemophilia patients: 304

- Age of patients:
  - Median age of hemophilia patients: 13.3 years
  - No of patients under 10 years: 134 patients

- No of patients under prophylaxis: 47
  - LDP: 16 (mean age: 6.3 years)
  - Emicizumab: 31 (mean age: 18.6 years)
  - Indications for Emicizumab prophylaxis
    - Inhibitors: 7
    - ABR>8 : 16
    - IC bleeding: 4
    - GI bleeding: 4

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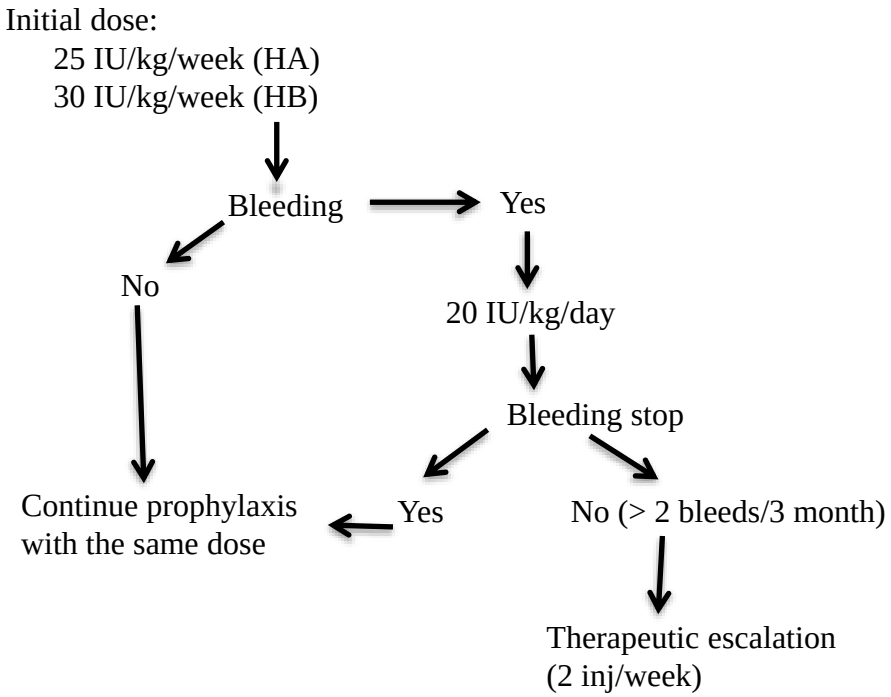
Prophylaxis protocol

Low dose prophylaxis



Prophylaxis with Emicizumab

Induction phase : 3 mg/kg/week for 4 weeks

Followed by

Maintenance phase: 6 mg/Kg/4 weeks

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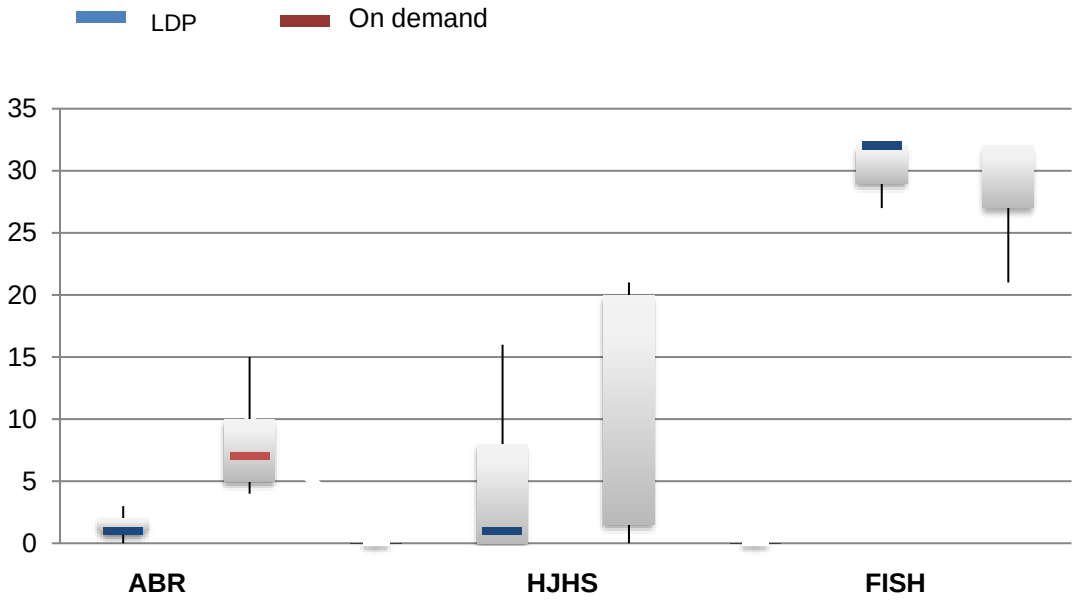
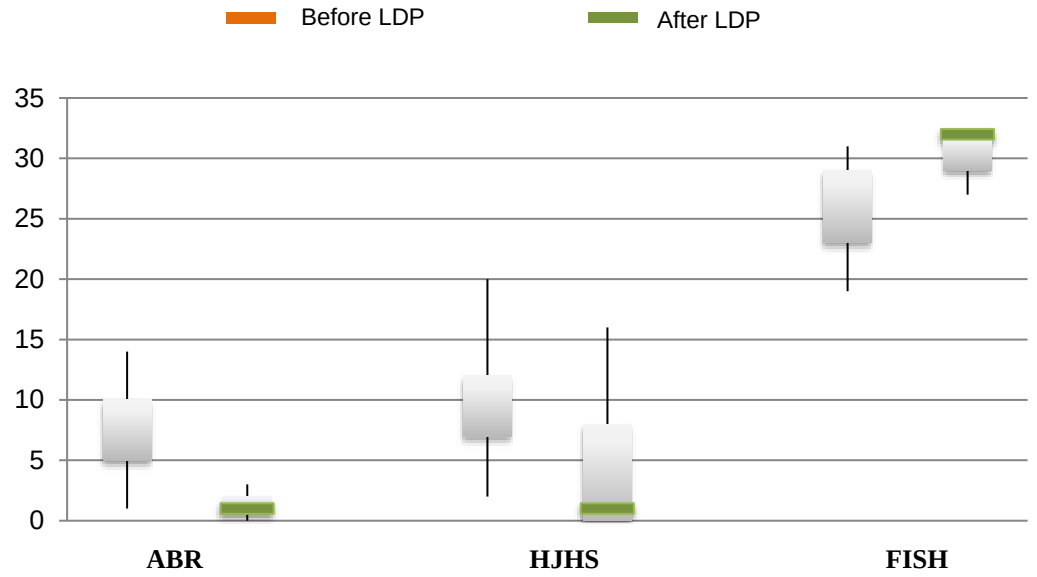
Results of LDP program



Comparison of ABR, HJHS, and FISH in patients on LDP (n=15) and on-demand treatment (n=16) after a 3-year follow-up.



Comparison of ABR, HJHS and FISH in 15 patients on LDP before and after a 3 year follow-up

- Compliance on selected patients: 89.5%
- 71% of patients live out of Dakar
- Inhibitor incidence: 20%

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Current challenges and barriers for implementing prophylaxis in Senegal

- Delay on prophylaxis initiation (6.3 years)

- 65% of eligible patients did not benefit from LDP for many reasons:
  - living in a residence far away from health service,
  - parents' lack of motivation for regular follow-up,
  - fears of additional out-of-pocket healthcare costs.

Expectations for the next 5 years

- More social support from the authorities
- improvement of geographic and financial accessibility to care for PWH. *(the challenge is not only availability of CFC)*
- Training on home treatment
- More use of Emicizumab will likely encourage patient acceptance of prophylaxis by reducing the patient dependence on the health care system
- Inclusion on gene therapy clinical trials

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STORY OF LOW DOSE PROPHYLAXIS IN TUNISIA

Emna Gouider, MD

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Speaker disclosures

NONE

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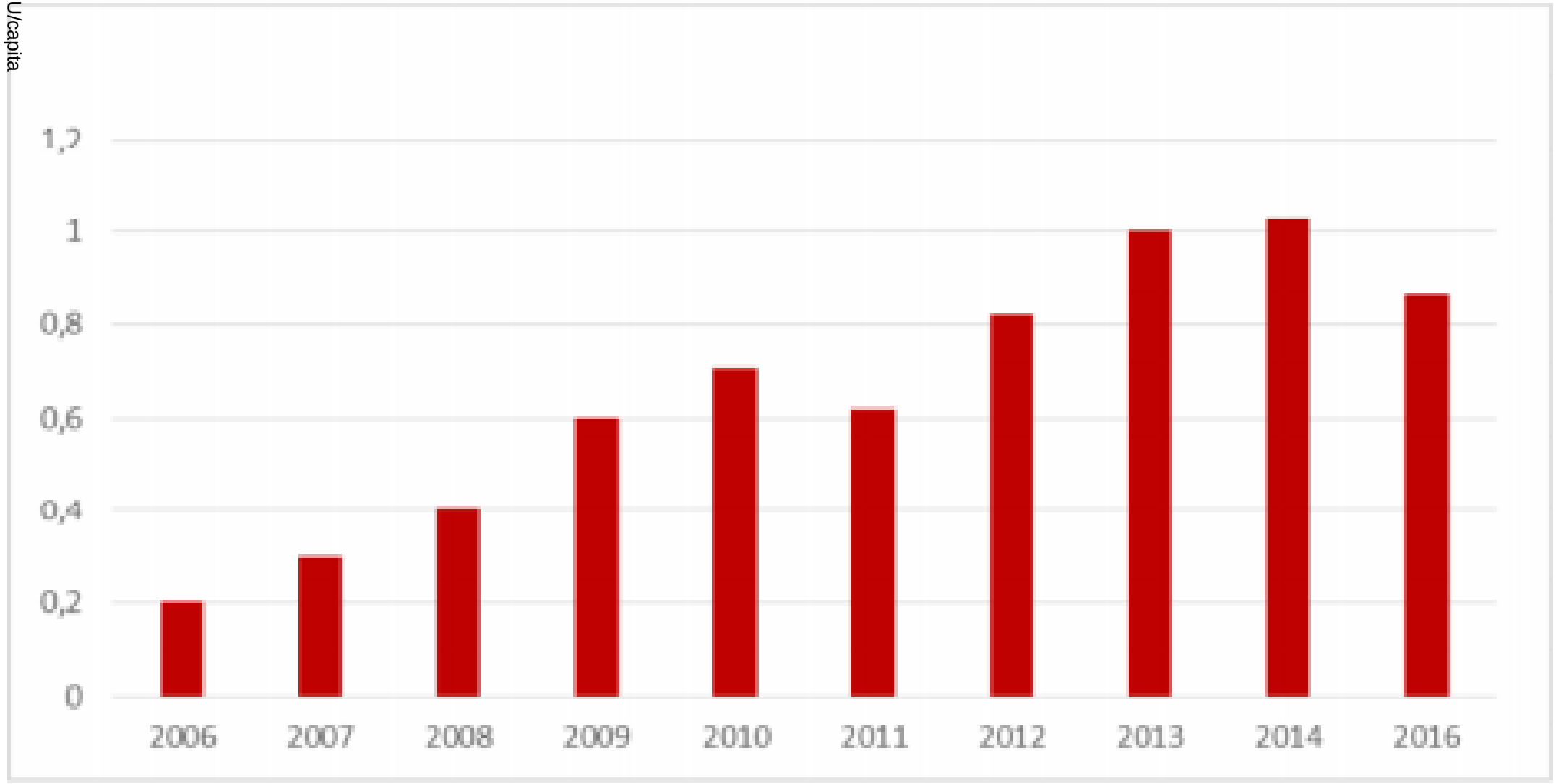
Hemophilia in Tunisia



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Low dose prophylaxis in Tunisia

First step

Child, 3 years old bleeding frequently (3 times/week)

Why not using the amount of FVIII for episodic treatment for a protocol of low dose prophylaxis?
15 UI/kg x3/week

Excellent evolution: no bleeding, less mother's anxiety

Low dose prophylaxis in Tunisia

Second step

All children bleeding frequently received a LDP regimen of 10-15 UI/kg twice or thrice a week according to facilities

All children going to school

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Low dose prophylaxis in Tunisia

Third step

Exchanges of experiences

Start with primary prophylaxis

Start also prophylaxis for some adults

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Hematologist
Biologist
Physiotherapist
Nurse
Pharmacist

Orthopedist
Surgeon
Dentist

Patients
&
Parents

NMO

WFH

LOW DOSE PROPHYLAXIS

TUNISIA, step by step….

1

2007

Episodic treatment

0.25 U/capita

2

2014

50 children on low dose prophylaxis

3

2015

Low dose prophylaxis in other HTC

Prophylaxis for some adults

Prophylaxis for PWH and inhibitor

4

2016

ITI for PWH and inhibitor

5

2023

Extended half life product?

Full dose prophylaxis?

6

2025

Emicizumab?

New drugs?

……

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STRENGTH

NMO & HEALTH CARE PROVIDER WORK TOGETHER SUPPORT OF WFH

WEAKNESS

SOME DISPARITY BETWEEN HTC IN THE COUNTRY

OPPORTUNITY

EASIER TO IMPROVE PROPHYLAXIS and ACCESS TO NEW TREATMENT, EXCHANGE EXPERIENCES AND CHALLENGES

THREATS

POLITICAL INSTABILITY

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1 HEALTHCARE PROVIDER

2 PATIENTS AND PARENTS

3 NMO & WFH

4 GOVERMENT

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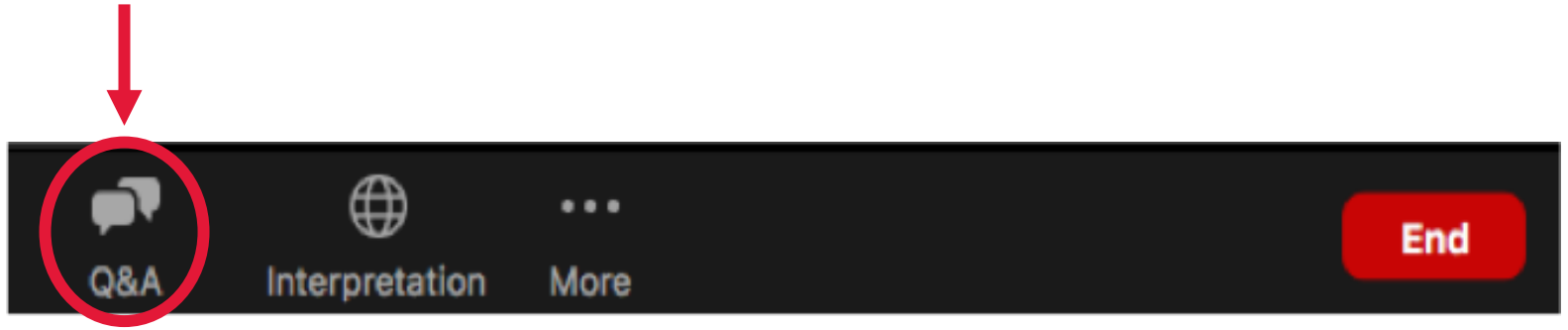
PANEL DISCUSSION

Please submit any questions in the Q&A box



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This webinar was part of a series. The next sessions will be taking place on the following dates:

- **Tuesday, October 12, 2021 from 8AM to 10AM ET**
- **Thursday, December 16, 2021 from 8AM to 10AM ET**

Registration will be open soon.

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COMPASSION to ACTION
Together we can

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¡GRACIAS!

MERCI!

شكرا

СПАСИБО

STAY SAFE!

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