Bleeding disorders and Ageing - Emerging Clincial Issues

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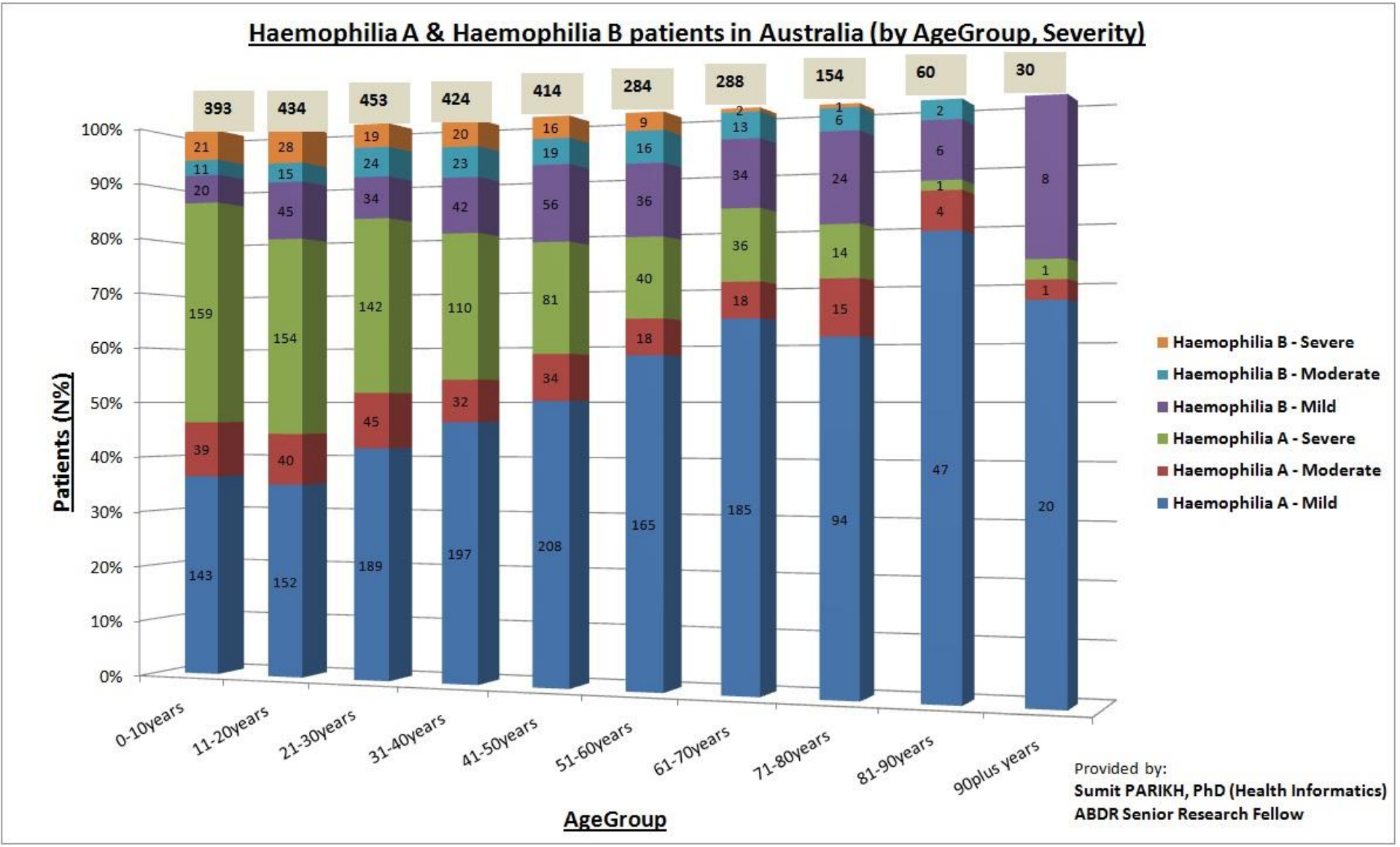
Global Ageing

https://www.who.int/news-room/fact-sheets/detail/ageing-and-health

- By 2020, the number of people aged 60 years and older will outnumber children younger than 5 years.
- By 2050, the world's population aged 60 years and older is expected to total 2 billion
- All countries face major challenges to ensure that their health and social systems are ready to make the most of this demographic shift.
- A longer life brings with it opportunities, not only for older people and their families, but also for societies as a whole.
- There is no "typical" older person.

Age distribution of patients with Haemophilia in Australia (2019)



Provided by:
Sumit PARIKH, PhD (Health Informatics)
ABDR Senior Research Fellow

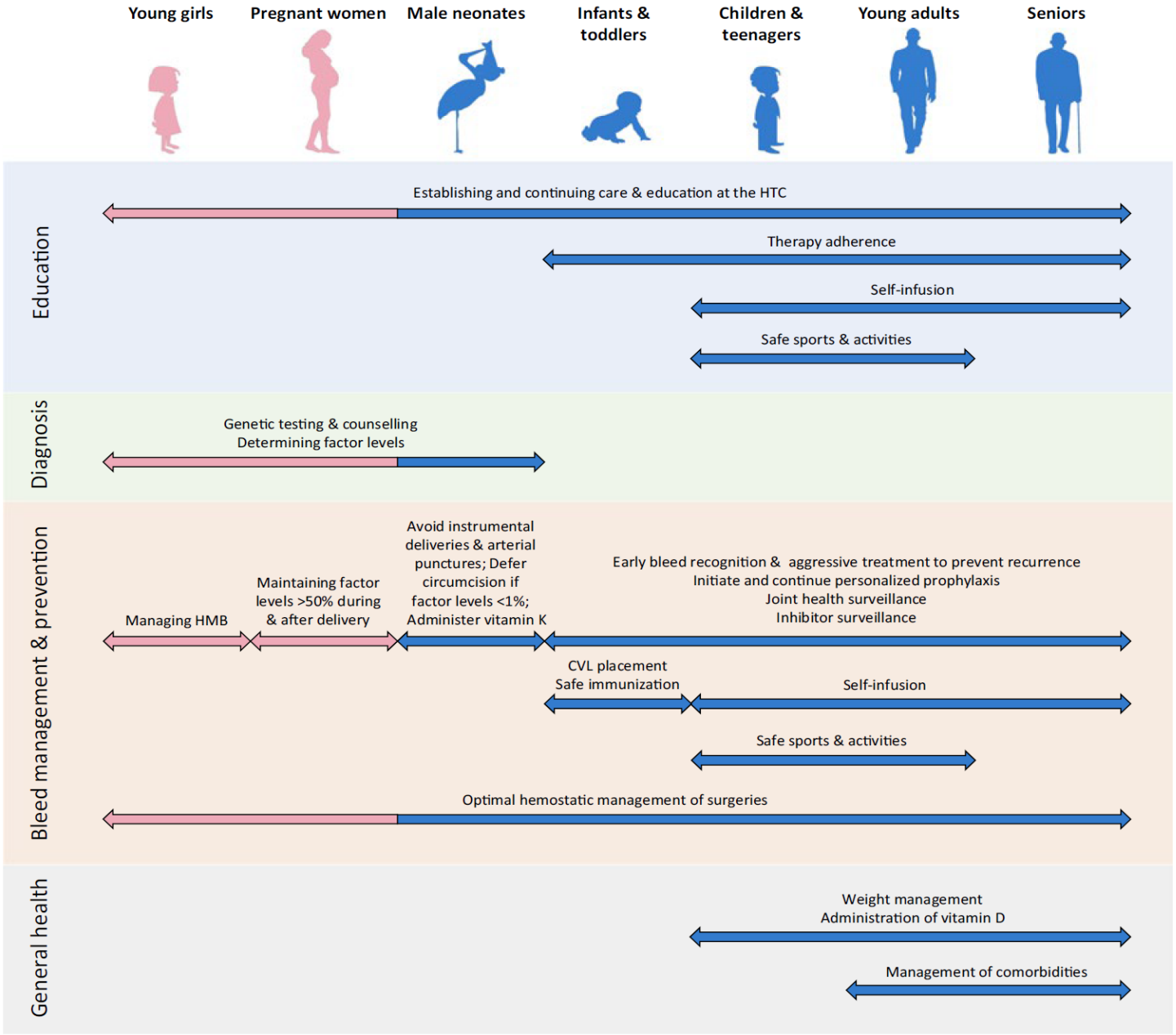
Ageing and Haemophilia

Advances in the development of effective and safer treatments for haemophilia over the last 50 years have resulted in a significant increase in the life expectancy of persons with haemophilia and other bleeding disorders

Life expectancy for persons with hemophilia has increased significantly from 11.4 years in 1920 to a potentially normal life span today[1,2]

As life spans normalize with adequate haemophilia care, people with inherited bleeding disorders are now transitioning from a focus primarily on bleeding and its complications to a focus that includes health promotion and disease prevention.

1,2 : Shapiro and Makris, British Journal of Haematology, 2019, 184, 712–720; Larsson, S.A. British Journal of Haematology, 1985,59, 593–602.



Gupta and Shapiro British Journal. Haemophilia. 2018; 24 (suppl. 6): 76-86.

Key issues faced by ageing persons with haemophilia
- Directly related to haemophilia and realated to general ageing

Issues faced by ageing PWH	Recommendations for management*
Chronic arthropathy and loss of bone mineral density	Regular review by a physiotherapist specialising in haemophilia
	Offer COX-2 inhibitor rather than NSAIDs for pain control when needed, use lowest effective dose and consider additional proton-pump inhibitor
	Measure bone mineral density in PWH who have significant arthropathy
	Do not routinely give vitamin D supplementation
Bleeds and risk of inhibitors	Consider regular prophylaxis as opposed to 'on demand' therapy for people with severe bleeding phenotype
	Remain vigilant to risk of inhibitor formation, particularly in patients with moderate-mild haemophilia
Hepatitis C, cirrhosis, hepatocellular carcinoma	Offer all PWH who have active hepatitis treatment to clear HCV with the newer agents as appropriate
	PWH who had cirrhosis before they cleared HCV, remain at risk of hepatocellular carcinoma and require regular hepatology follow-up with liver ultrasound and alpha-fetoprotein monitoring
HIV	PWH should be under the care of a physician specialising in HIV
Cardiovascular disease (hypertension, ischaemic heart disease, atrial fibrillation)	*Prevention*:
	Educate patients with regards to cardiovascular risk and encourage and support interventions to reduce this risk (smoking, obesity, exercise, hypertension, cholesterol)
	Treatment:
	Manage patients on an individualised basis following multidisciplinary team discussion and counselling. Where possible, minimise the duration and intensity of antiplatelet/anticoagulant medications
Malignancy	Provide haemostatic cover for invasive investigations including biopsy and surgery
	Oncology treatments, such as chemotherapy, should not be withheld; haemostatic replacement may be required during periods of thrombocytopenia
Renal disease	Check renal function at least annually
	For patients with haematuria, consider urology referral for patients with mild haemophilia, recurrent haematuria, and elderly patients
Sexual dysfunction	Be alert to this issue. Referral to specialists or general practitioners may be required
Depression, dementia	Screen for depression at clinic visits. Offer appropriate support and referral
Reduced mobility, dexterity, and visual acuity	Screen for mobility problems at clinic visits in order to offer proactive MDT support
Reduced access to health care, ability to self-treat	Be alert to changes at clinic visits in order to offer support through MDT and community teams

Shapiro and Makris, British Journal of Haematology, 2019, 184, 712–720;

Ageing, Health Risks and Other co-morbidities
: Cardiovascular Disease

Cardiovascular disease (CVD) management is challenging, having to manage anticoagulants; anti-platelet agents and cardiac surgery – all associated with increase bleeding risk.

Encouraging risk reduction and optimising other factors

- Smoking cessation
- Hypertension management
- Hyperlipidaemia management
- Type 2 diabetes management
- Overweight/Obesity management

"High blood pressure, high cholesterol, high blood sugar, high anxiety...getting high is no fun at my age!"

Makris M et al. J tjhromb Haemost. 2012; 10; 20-22. Schutgens RE et al. Blood. 2016. 128; 2471-2474;

Case 1

- 50 yo male, ~ 70kg
- Type 2 VWD; strong family history
- No issues with spontaneous bleeds; Biostate for procedures

Other Health Issues:

- Interstitial lung disease
- Hypercholesterolaemia
- Hypertension
- Coronary artery disease
- Chronic kidney disease

Medications: atorvastatin, seretide, olmesartan, amlodipine, pantoprazole.

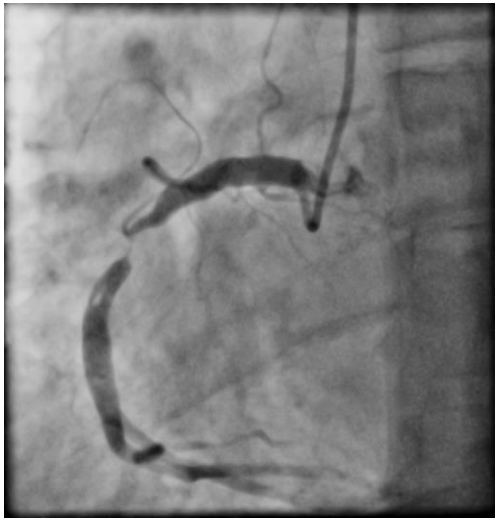
Case 1

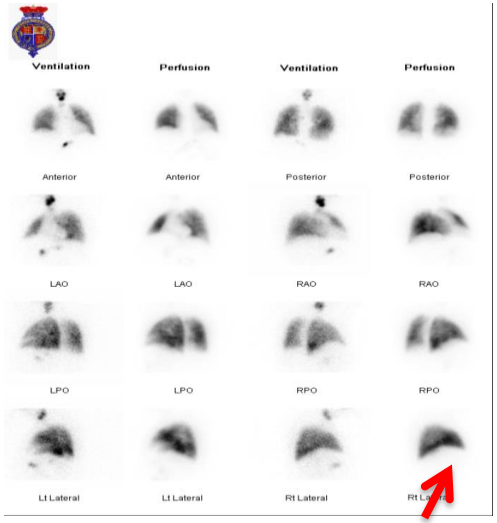
Presented to Emergency after having fainted, recently returned from overseas

- ST depression on ECG : diagnosis **NSTEMI (myocardial infaction, heart attack)**

But… also short of breath

- **Pulmonary Embolism (**Blood clot in both sides of the lung)





- Bare Metal Stent inserted into blocked artery
- Triple therapy (Clopidogrel, Asprin, Warfarin)

Case 1

Anticoagulated:

- Warfarin (3 months)
- Aspirin 100 mg daily (6 weeks)
- Clopidogrel 75 mg daily (ongoing)

Twice weekly Biostate : for 3 months while on warfarin and Clopidogrel.

Biostate now only for procedures

Ageing, Health Risks and Other co-morbidities
: Overweight/Obesity

Body mass index (BMI) between 25 and 29.9 are overweight, and those with a BMI of 30 and above are obese.

The National Public Health Surveillance in the US found **34.1%** of persons with bleeding disorders to be overweight and **22.7%** to be obese, compared with age-matched controls.

Obesity in persons with haemophilia contributes negatively to joint health with increase bleeds and immobility and and impaired healing after orthopaedic surgery.

Exercise is beneficial : promotes health joints, muscle tone, optimal body weight, bone density and quality of life.

Soucie JM *et al*, Haemophilia. 2011; 17: 196-203; Soucie JM et al , The Universal Data Collection Surveillance system for rare bleeding disorders, 2011; Tuinenburg A et al. Haemophilia 2013;19: 744-752. Von Mackensen S *et al*. Haemophilia. 2-16. 22: 521-530. Souza JC *st al*. Int J Sports Med. 2012. 33; 83-88.

Ageing, Health Risks and Other co-morbidities :
Musculoskeletal Issues

- Chronic haemophilic arthropathy.
- Reduced bone mineral density (BMD), 2/3 of patients with moderate or severe haemophilia older than 50 years having osteoporosis
- Risk of falls/fractures and other injuries

Multi-disciplinary approach : Assessment for sensory changes, balance, mobility changes, and circulatory impairment will lead to practical recommendations.

Surgical management, i.e. joint replacement

- Osteoarthritis
- Re-do surgeries

Iorio A. et al. Thrombosis and Haemostasis. 2010. 103; 596-603. Kiper Unal HD. American Journal of Blood Research. 2017. 7; 59 -66.

Ageing, Health Risks and Other co-morbidities : Cancer

Risk of malignancy in patients with bleeding disorders is similar to the general population

- except HCV associated liver cancer; and HIV related malignancy

Factor replacement for invasive investigations : biopsy and surgery

- planning and coordination with HTC

Chemotherapy should not be withheld; and factor replacement may be necessary if blood counts (platelets) drop

Dunn AL. Haemophilia. 2010. 16; 427-436. Astermark J. 2012. Haemophilia, 18; 664-671. Biron-Andreani C et al. 2014. Haemophilia 20; 78-82.

Case 2

54yo female

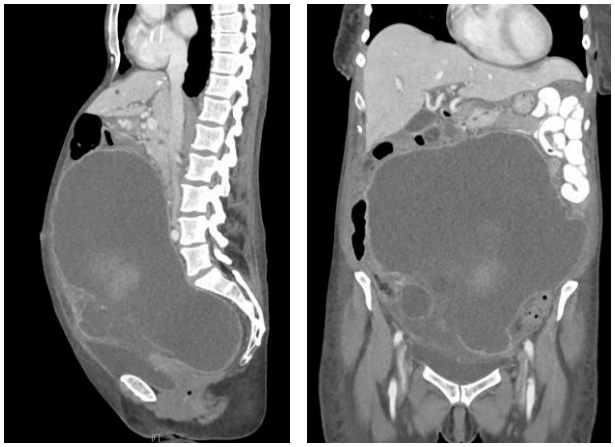
Type 2 VWD

Mild bleeding phenotype

- Dental extractions without cover
- No significant spontaneous bleeding

Several months: noticed increasing abdominal distension

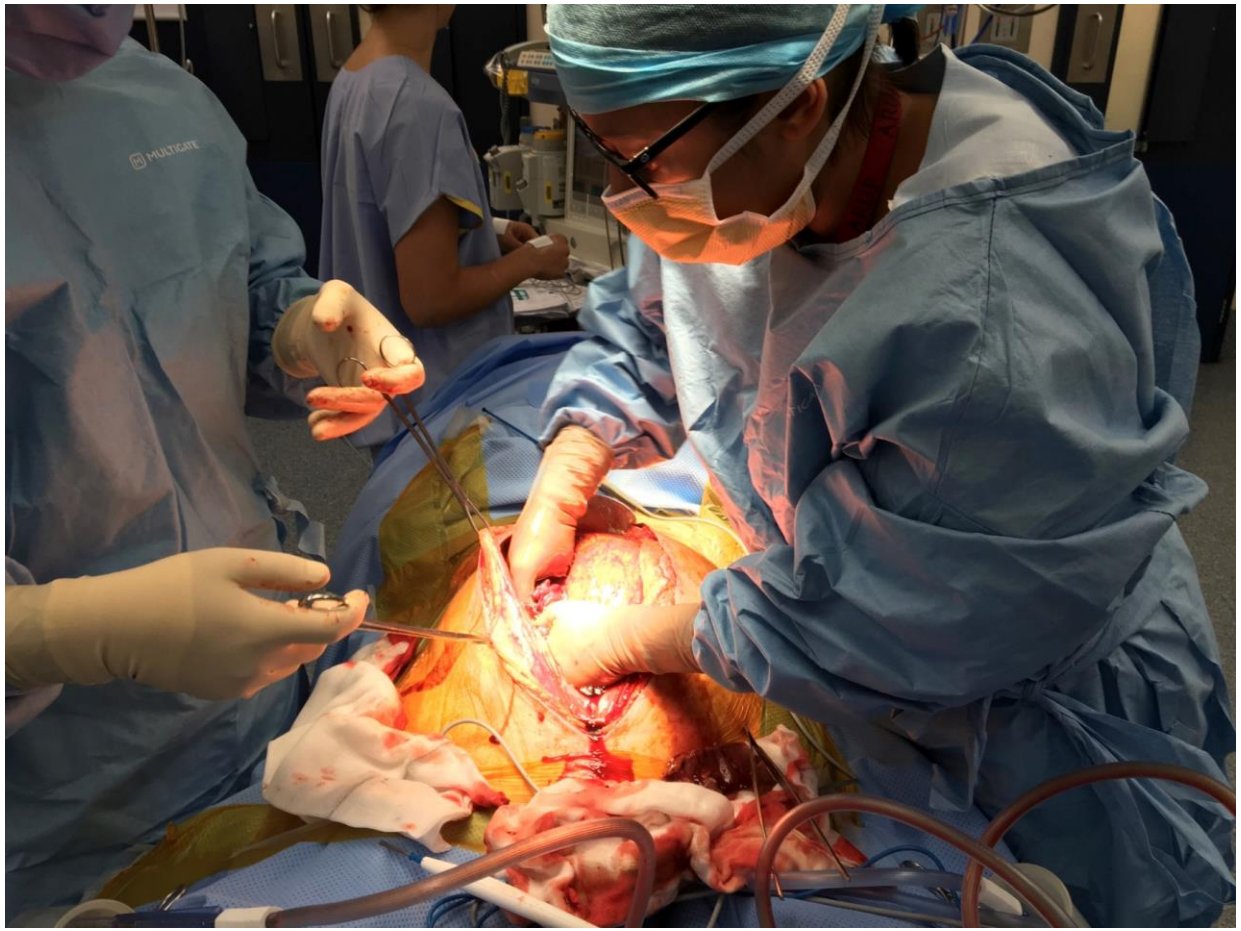
– Significant weight loss and anaemia



Diagnosis: Peritoneal mesothelioma
(a form of cancer that affects the lining of the abdomen)

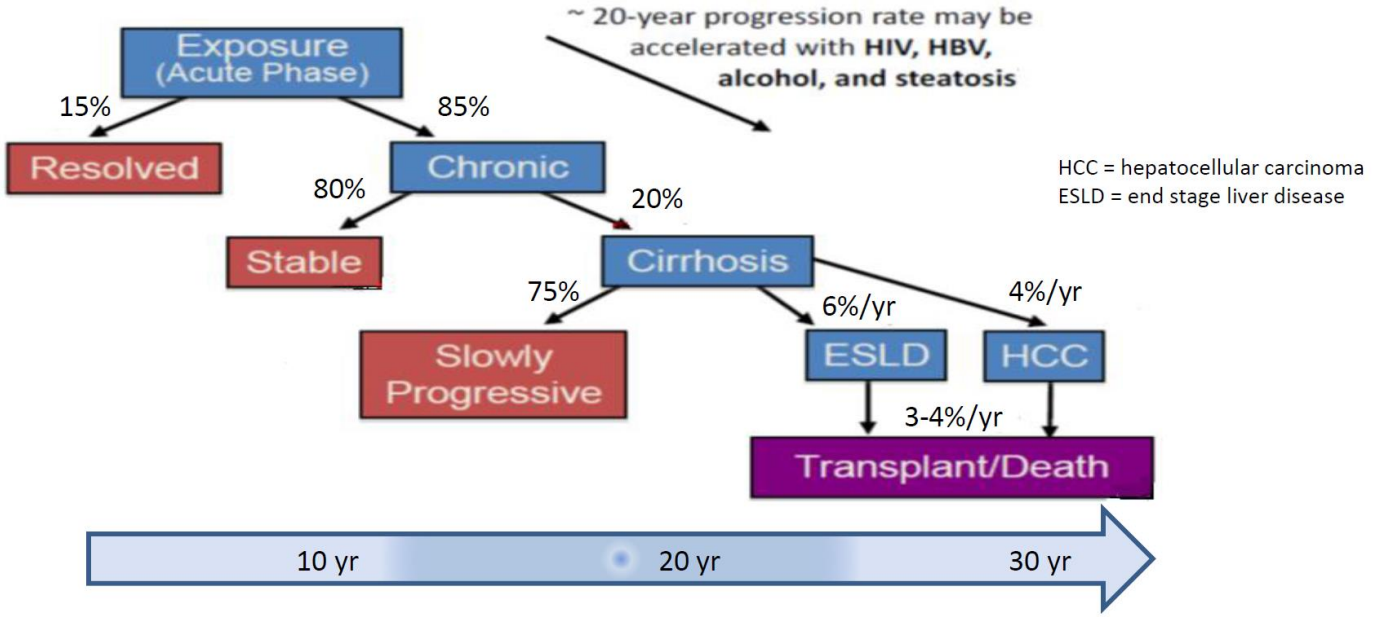
Case 2

Peritonectomy with Chemotherapy (12 hour operation)



Ageing, Health Risks and Other co-morbidities : Hepatitis C

Natural History of Hepatitis C Infection



Di Bisceglie AM. *Hepatology.* 2000;31(4):1014-1018. 2. Bialek SR, Terrault NA. *Clin Liver Dis.* 2006;10(4):697-715. 3. John-Baptiste A et al J Hepatol 2010; 53: 245-51

Ageing, Health Risks and Other co-morbidities : Hepatitis C

Prepared by the Australian Haemophilia Centre Directors' Organisation (AHCDO) and Haemophilia Foundation Australia (HFA), August 2017

Many Australians with haemophilia, VWD and other bleeding disorders acquired Hep C (HCV) through blood products for their treatment before 1993, usually though plasma-derived clotting factor concentrates

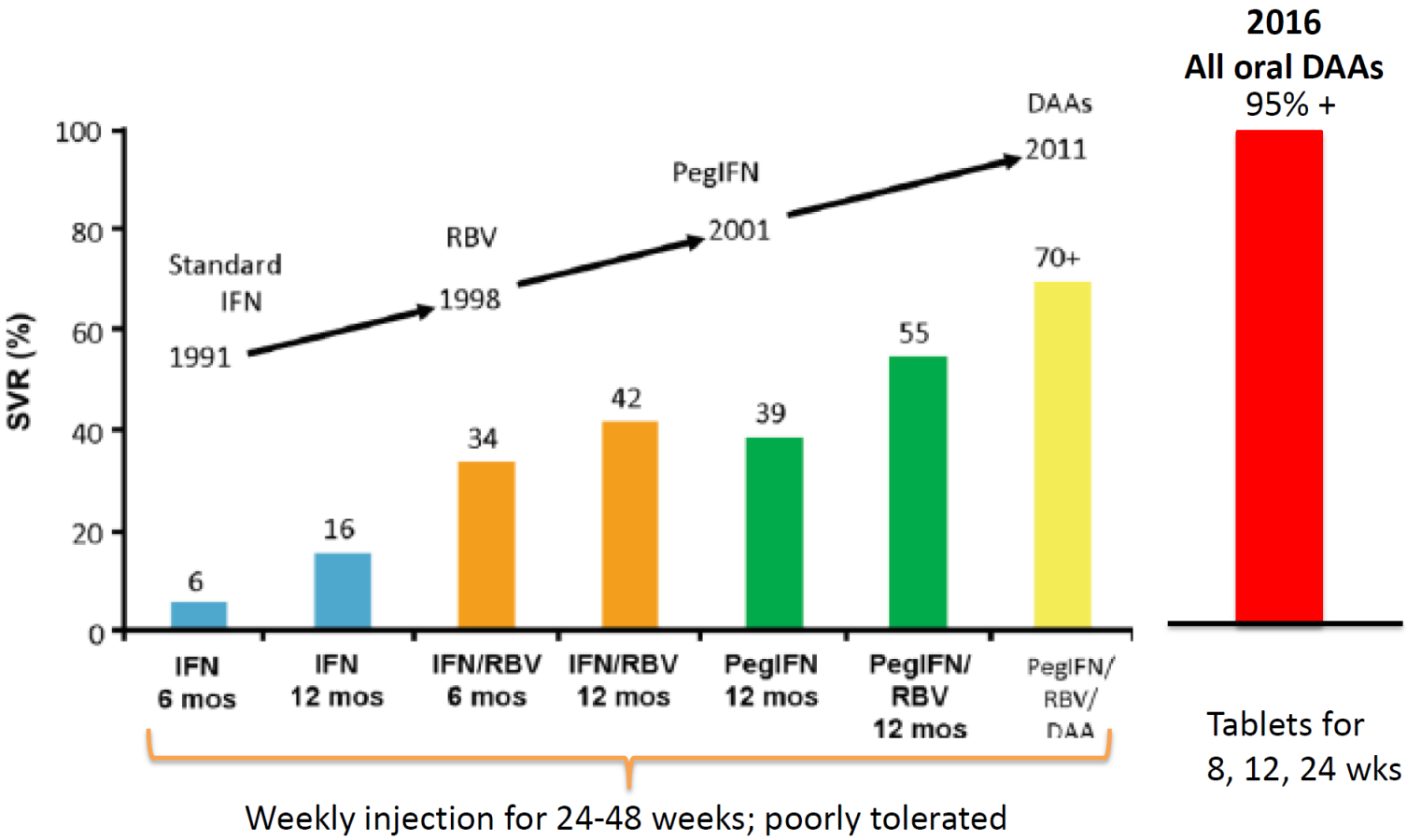
Treatment for Hep C: clear the virus and prevent progression to cirrhosis and end stage liver disease

Ongoing follow up : risk of cirrhosis and HCC even if Hep C cleared

Fransen van de Putte. *et al.* 2014. Journal of Hepatology, 60; 39 -45.

Ageing, Health Risks and Other co-morbidities : Hepatitis C

HCV Treatment



DAA: direct-acting antiviral agents

Slide : Professor Martin Weltman, Hepatologist, Nepean Hospital.

Ageing, Health Risks and Other co-morbidities : Hepatitis C

New direct-acting antiviral (**DAA**) therapies for HCV are highly effective (high cure rates), easier to administer and available for all Australians with HCV. The WHO has a goal of eliminating HCV by 2030; and Australia is well placed to achieve this.

Clinical management of persons with a bleeding disorder and HCV should be the same as for the general population :

- Australian recommendations for the management of hepatitis C
- Considerations to manage potential bleeding complications in patients with advanced liver disease
- Management of advanced liver disease should be in conjunction with a liver specialist and HTC.

Hepatitis C Virus Infection Consensus Statement Working Group. Australian recommendations for the management of hepatitis C virus infection: a consensus statement. Melbourne: Gastroenterological Society of Australia, August 2017.

Clinical guidance for treating hepatitis C virus infection: a summary

Six key questions before commencing treatment for hepatitis C virus (HCV) infection

- Is cirrhosis present?
- What is the HCV genotype?
- Is the patient treatment-naive?
- Is HBV–HCV or HIV–HCV coinfection present?
- Are there potential drug–drug interactions?
- What is the renal function (eGFR)?

Checklist for pre-treatment assessment for people with hepatitis C virus (HCV) infection

	HCV virology: • Anti-HCV (serology) • HCV PCR • HCV genotype, quantitative HCV RNA level*	 • Indicates HCV exposure • Confirms HCV infection • May influence choice and duration of treatment regimen
	HCV treatment history — previous regimen and response	Determines treatment regimen and duration
	Potential for non-adherence?	Consider medical and social issues that may be barriers to medication adherence
	Alcohol intake history	Cofactor for cirrhosis
	Check for drug–drug interactions	**www.hep-druginteractions.org** Includes prescribed, over-the-counter, herbal, illicit drugs
	Pregnancy discussion†	
	Weight and body mass index	Non-alcoholic fatty liver disease is a cofactor for cirrhosis
	Signs of chronic liver disease	
	FBE	• Baseline haemoglobin level • Low platelets — suspect portal hypertension
	LFTs and INR	Low albumin, raised bilirubin, raised INR suggest advanced cirrhosis
	U&Es and eGFR	• Sofosbuvir is not recommended if eGFR < 30 mL/min/1.73 m^2 • Ribavirin is renally cleared and needs dose reduction if eGFR < 50 mL/min/1.73 m^2
	HBV (HBsAg, anti-HBc, anti-HBs), HIV, HAV serology	Specialist referral is recommended for people with HBV or HIV coinfection If seronegative, vaccinate against HAV, HBV
	Cirrhosis assessment • e.g. FibroScan • e.g. APRI	Thresholds consistent with no cirrhosis: • Liver stiffness < 12.5 kPa • APRI < 1.0 Specialist referral is recommended for people with cirrhosis
	Electrocardiogram if ribavirin therapy planned and patient is aged > 50 years OR has cardiac risk factors	Screen for ischaemic heart disease

FBE = full blood examination. LFT = liver function test. INR = international normalised ratio. U&E = urea and electrolyte. eGFR = estimated glomerular filtration rate. HBV = hepatitis B virus. HAV = hepatitis A virus. HBsAg = hepatitis B surface antigen. anti-HBc = hepatitis B core antibody. anti-HBs = hepatitis B surface antibody. APRI = aspartate aminotransferase to platelet ratio index. MELD = Model for End-Stage Liver Disease. HCC = hepatocellular carcinoma. * HCV genotype is required by the PBS criteria; it is important before prescribing elbasvir plus grazoprevir or sofosbuvir plus ledipasvir. HCV RNA level is important for determining eligibility for 8-week treatment duration with sofosbuvir plus ledipasvir. † As there are no safety data for the use of any direct-acting antiviral regimen during pregnancy, treatment of pregnant women is not recommended. Ribavirin (Category X) and peginterferon-alfa are contraindicated during pregnancy.

Support for people living with hepatitis C

People living with hepatitis C can receive information, support and referral from community services, including:

- Hepatitis Australia: http://www.hepatitisaustralia.com
- Hepatitis Information Line: 1800 437 222
- Australian Injecting & Illicit Drug Users League: http://www.aivl.org.au

On-treatment and post-treatment monitoring for virological response

Routine monitoring for an 8–12-week treatment regimen:

Week 0	• Pre-treatment blood tests, including LFTs, HCV PCR
Week 12 post-treatment (SVR)	• LFTs, HCV PCR (qualitative)

- More intensive monitoring may be required in certain populations (see *Australian recommendations for the management of hepatitis C virus infection: a consensus statement* (September 2018), http://www.gesa.org.au).
- People treated with elbasvir plus grazoprevir should have LFTs at Week 8 to screen for hepatotoxicity.

SVR = sustained virological response at least 12 weeks after treatment (cure). LFT = liver function test. INR = international normalised ratio. HCV = hepatitis C virus. PCR = polymerase chain reaction.

Ongoing monitoring of people after successful hepatitis C treatment outcome (SVR)

SVR, no cirrhosis and normal LFT results (males, ALT < 30 U/L; females, ALT < 19 U/L):

- People who are cured do not require clinical follow-up for hepatitis C

SVR and abnormal LFT results (males, ALT ≥ 30 U/L; females, ALT ≥ 19 U/L):

- Patients with persistently abnormal LFT results require evaluation for other liver diseases and should be referred for gastroenterology review. Investigations to consider include: fasting glucose level, fasting lipid levels, iron studies, ANA, ASMA, anti-LKM antibodies, total IgG and IgM, AMA, coeliac serology, copper level, caeruloplasmin level and α-1-antitrypsin level

SVR and cirrhosis:

- Patients with cirrhosis require long-term monitoring and should be enrolled in screening programs for:
  - hepatocellular carcinoma
  - oesophageal varices
  - osteoporosis

SVR = sustained virological response at least 12 weeks after treatment (cure). LFT = liver function test. ALT = alanine aminotransferase. ANA = anti-nuclear antibodies. ASMA = anti-smooth muscle antibodies. LKM = liver–kidney microsome. AMA = anti-mitochondrial antibody.

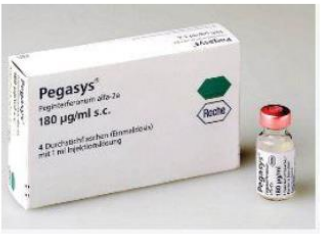
People who do not respond to hepatitis C treatment

- Specialist referral recommended

Updated September 2018

GESA Gastroenterological Society of Australia
ala Australian Liver Association
AUSTRALASIAN HEPATOLOGY ASSOCIATION
ASID
ashm Supporting the HIV, Viral Hepatitis and Sexual Health Workforce
hepatitis australia

Hepatitis C Medications



Drug	Name	Dose of each tablet	
Daclatasvir	Daklinza	60 mg	BMS
Sofosbuvir	Sovaldi	400 mg	Gilead
Ledipasvir / Sofosbuvir	Harvoni	90 mg / 400mg coformulated	Gilead
Zepatier	Grazoprevir Elbasvir	100 50 mgmg	MSD
Ribavirin	Ibavyr	400 mg or 600 mg	Clinect
Ombitasvir/Paritaprevir/ritonavir Dasabuvir	Viekira Pak Viekira Pak-RBV	12.5mg/75mg/50mg coformulated 250mg Includes Ribavirin 200mg or 400mg or 1000mg or 1200mg	Abbvie
Peginterferon alfa-2a	Pegasys	180 mcg SCI once weekly	Roche
Peginterferon alfa-2b	Pegatron	1.5 mcg/kg SCI once weekly according to weight	MSD

Slide : Professor Martin Weltman, Hepatologist, Nepean Hospital.

HFA's recent strategy was to encourage treatment as a priority

TITLE

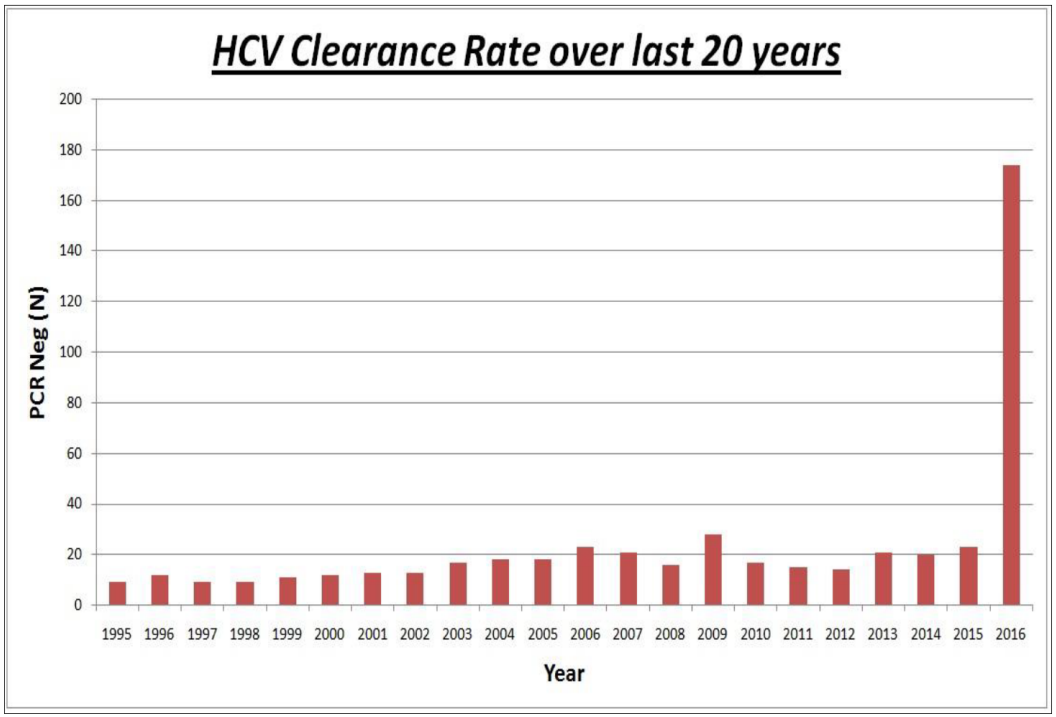
Uptake of subsidised Hepatitis C direct acting antiviral treatment among patients with bleeding disorders in Australia

Sumit PARIKH[1] ,Simon McRAE[1,2], Huyen TRAN[1,3] [Email: S.Parikh@ahcdo.org.au]

[1]Australian Haemophilia Centre Director's Organisation (AHCDO), [2]Royal Adelaide Hospital, Adelaide, Australia, [3]The Alfred Hospital, Melbourne, Australia

Topic: Outcome Research (Poster #78)

Presented at WFH 2018



Ongoing Advocacy HFA's recent strategy:

Treatment as a priority:

- National clinical management consensus guidelines on who to test for hepatitis C virus now include 'people with coagulation disorders who received blood products or plasma-derived clotting factor treatment products before 1993'.

- AHCDO and HFA collaborated with hepatitis experts to produce a fact sheet for general practitioners on people with bleeding disorders and hepatitis C.

- HFA's World Hepatitis Day campaign has included messages for family and friends to pass on to those affected, with compelling personal stories about treatment; cure and importance of followup..

- HFA continues to work with Hepatitis Australia and other hepatitis research organisations on wider community strategies to promote testing and treatment to people with hepatitis C.

- Getting Older Project (Preetha Jayaram): Ongoing impact of Hep C

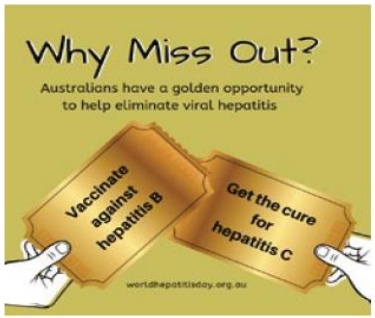
HFA World Hepatitis Day :

- Elimination campaign
- Patients to make sure their HTC had their latest results for their hep C treatment
- Check if they need follow-up liver health testing (eg if they have cirrhosis)

WORLD HEPATITIS DAY

World Hepatitis Day is marked globally on 28 July. The World Hepatitis Alliance has committed to eliminating viral hepatitis by 2030.

Imagine a future without hepatitis C. Can we achieve this in the Australian bleeding disorders community?



HAVE YOU BEEN CURED?

The new hepatitis C treatments can cure nearly everyone and have few, if any, side-effects.

Haemophilia Treatment Centres are currently collecting data to check which of their patients have been cured of their hep C and their current liver health. You can help this work by making sure your HTC has your results for:

- your hepatitis C treatment
- your latest HCV PCR test
- your most recent liver health test/ fibroscan.

Ask your hepatitis specialist or GP if you need follow-up for your liver health. For example, if you have cirrhosis and have successful treatment, you will still need to have liver health checks regularly.

Many people with bleeding disorders have been treated and cured but some might not even know they have hep C.

YOU COULD BE AT RISK

- If you ever had a blood product for treatment before 1993 – even as a baby
- If you have shared equipment that allows blood from an infected person to enter your bloodstream, eg injecting equipment, non-sterile tattooing, medical care overseas
- Still wondering? Take the Hepatitis Risk Quiz to see if you are at risk - www.worldhepatitisday.org.au/quiz
- Is this you or someone you know? Have you ever been tested for hep C? If not, now is the time to be tested - and have treatment to be cured, if you do have hep C!

As a Partner in the national World Hepatitis Day Campaign, HFA works with Hepatitis Australia and State and Territory Foundations on the annual national awareness campaign and is committed to making a difference on hepatitis C in Australia.

FOR MORE INFORMATION

Visit

- www.world.hepatitisday.org.au
- The HFA World Hepatitis Day page - https://tinyurl.com/HFAWHD19

Or talk to your hepatitis specialist, your HTC or your local doctor

National Haemophilia No. 207, September 2019

Ageing, Health Risks and Other co-morbidities : HIV

HIV-positive patients

- Under the care of HIV specialist physicians

- Almost all are on cART (combination anti-retroviral therapy)

Aims of cART

- **Durable suppression of HIV replication**
  - Plasma viral load
  - Permits recovery/preservation of immunological function
- **Reduce HIV-associated morbidity & maintain quality of life**
  - E.g. opportunistic infections & malignancies
- **Minimised treatment-related toxicities**
  - Drug safety (including drug-to-drug interactions)
- **Expanded aims/indications**
  - Prevention of transmission ('Undetectable=Untransmissible')

Dr Fred Lee, Immunologist, RPA

Ageing, Health Risks and Other co-morbidities : HIV

Key ART Classes

Nucleos(t)ide reverse transcriptase inhibitors (NRTIs) • Abacavir • Tenofovir	**Non-nucleoside reverse transcriptase inhibitors (NNRTIs)** • Nevirapine • Efavirenz
Protease inhibitors* (PIs) • Darunavir • Atazanavir **require pharmacokinetic boosting*	**Integrase strand transfer inhibitors (INSTIs)** • Raltegravir • Dolutegravir

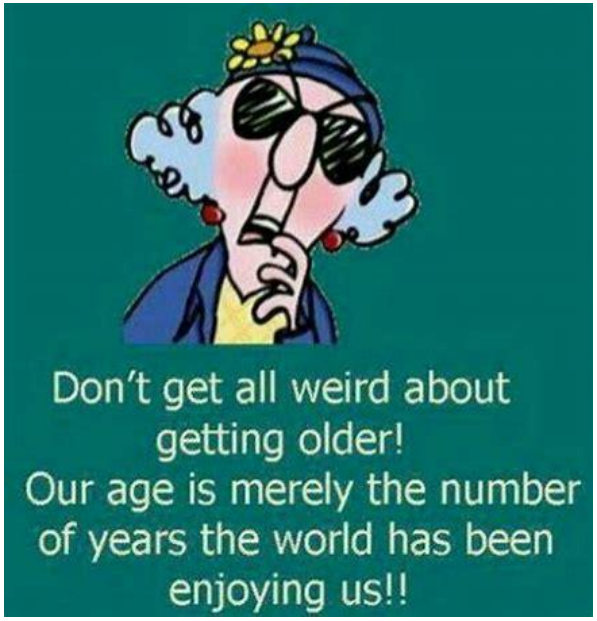
Dr Fred Lee, Immunologist, RPA

Aim for 3 effective anti-retroviral therapy agents – minimise risk of emergent resistance mutations.

Summary:

As life spans normalize with adequate treatment

- care not only focusing on bleed prevention and management
- focus that includes health promotion and disease prevention



- Good collaboration with general practitioners, other specialists and HTC is important
- Still a lot of challenges, including viral transmitted infections
- Models of care need to focus on the ongoing needs of our patients
- Need adequate health and social systems

Thank you