

HBsAg loss and functional cure among people with chronic hepatitis B in Australia within the REACH-B study

**Hajarizadeh B¹, Nelson R², George J³, Cowie B^{4,5}, Davies J⁶, Hanson J^{1,7}, Martinello M^{1,8}, Brown T⁸, Wong I⁹, Hasan T⁹, Mascarenhas L¹⁰, O'Beirne J¹¹, Wade A¹², Capati M¹³, Trotter G¹⁴, Nash L¹⁴, Thomas S¹⁴, Allard N^{4,15}, Howard S¹⁴, Tu T^{3,16}, Tran L^{4,16}, Monaghan R¹, Carter J¹, Tu E¹, Erratt A¹, Dore G^{1,17}, Matthews G^{1,17},
on behalf of the REACH-B Study Group**

1. The Kirby Institute, University of New South Wales, Sydney; 2. The Queen Elizabeth Hospital and Royal Adelaide Hospital, Adelaide; 3. Storr Liver Centre, Westmead Hospital, and The Westmead Institute for Medical Research, University of Sydney, Sydney; 4. Royal Melbourne Hospital, Melbourne; 5. WHO Collaborating Centre for Viral Hepatitis, and the Peter Doherty Institute for Infection and Immunity, Melbourne; 6. Menzies School of Health Research, Darwin; 7. Cairns and Hinterland Hospital and Health Service, and Torres and Cape Hospital and Health Service, Cairns; 8. Justice Health & Forensic Mental Health Network NSW, Sydney; 9. Blacktown Mt Druitt Hospital, Sydney; 10. Utopia Refugee and Asylum Seeker Health, Melbourne; 11. Sunshine Coast University Hospital, Sunshine Coast; 12. Barwon Health, Geelong; 13. Top End Medical Centre, Darwin; 14. Western Australia Country Health Service, Perth; 15. Cohealth, Melbourne; 16. Hepatitis B Voices Australia, Melbourne; 17. St Vincent's Hospital, Sydney

Acknowledgements

The REACH-B study has been funded by the Department of Health and Aged Care.

Chief Investigator: Gail Matthews

Study Coordinator:

Principal Investigators & Protocol Steering Committee:

Jessica Carter

Greg Dore

Elise Tu

Behzad Hajarizadeh

Rob Monaghan

Jacob George

Lester Mascarenhas

Ben Cowie

Renjy Nelson

Jane Davies

James O'Beirne

Josh Hanson

Ian Wong

Thomas Tu

Tasnim Hasan

Lien Tran

Amanda Wade

Colette McGrath

Marianne Martinello

Tracey Brown

Georgina Trotter

Sarah Thomas

Lloyd Nash

Marilou Capati

Stephanie Howard

Nicole Allard

Isabelle Purcell



Background

- Although antiviral therapy for chronic HBV infection suppresses viral replication, hepatitis B surface antigen (**HBsAg**) **seroclearance (HBsAg loss)** remains a **key milestone and linked to functional cure**.
- **HBsAg loss** is associated with reduced risk of liver disease progression, hepatocellular carcinoma, and liver-related mortality.
- Clinical trials of novel antiviral agents use **functional cure as the primary treatment outcome**
- Real-world data on the incidence of HBsAg loss and functional cure among people with chronic HBV infection in Australia are limited
- We estimated the **incidence of HBsAg loss and functional cure** in the Australian Real-World Assessment of people living with Chronic Hepatitis B (REACH-B) study.

Methods

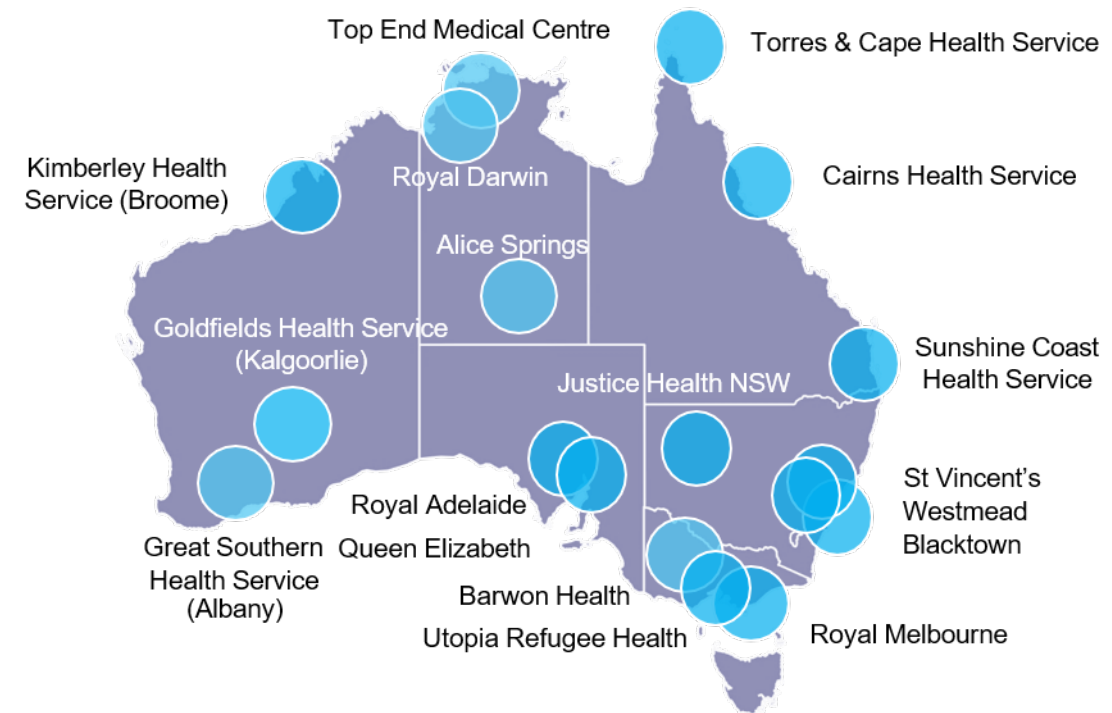
The Real-world Assessment of people living with Chronic Hepatitis B in Australia (*REACH-B Study*) is an observational cohort study of people living with chronic HBV in Australia attending a national network of hepatitis clinical services.

Study setting: 18 primary or tertiary health services in 6 jurisdictions:

NSW (4 sites)	Qld (3 sites)
SA (2 sites)	Vic (3 sites)
NT (3 sites)	WA (3 sites)

Study sites:

- Hospital-based clinics, n=15 (n=5 with community outreach)
- Primary care clinics, n=2
- Justice Health clinic, n=1



Methods

Data collection: Demographic, clinical care, treatment, and laboratory data are collected from medical records

Data are collected at:

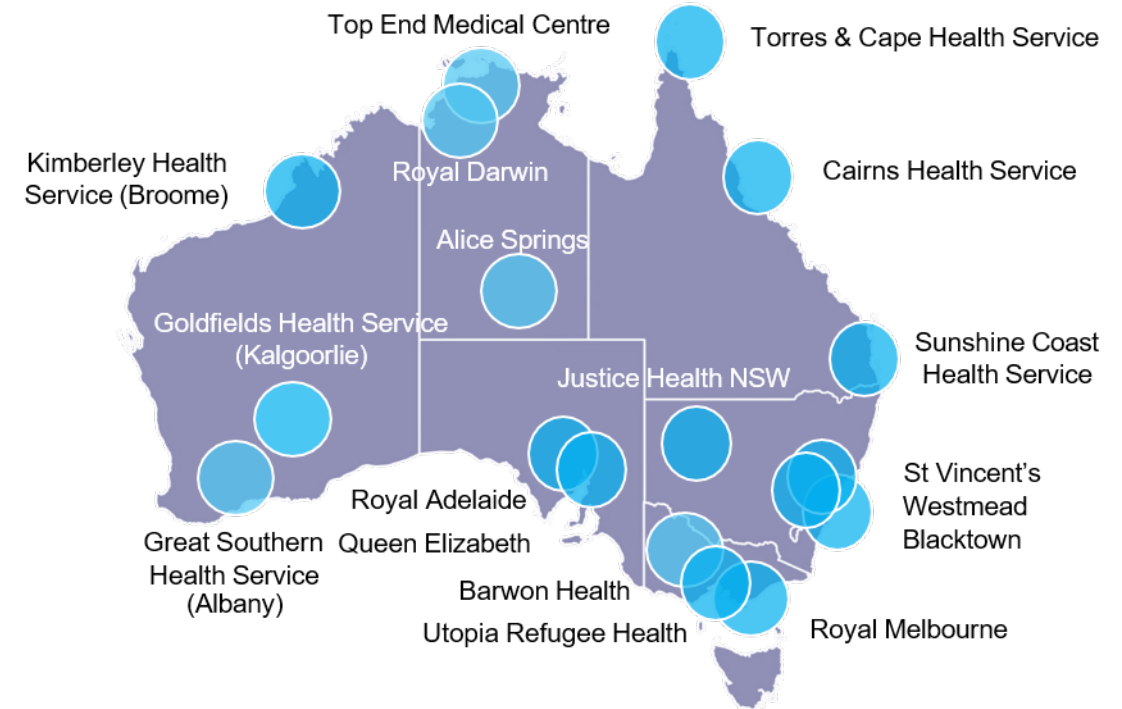
- Enrolment; and
- Follow-up visits (every 6-12 months)

This analysis included participants with a documented positive HBsAg at enrolment and ≥ 1 follow-up test.

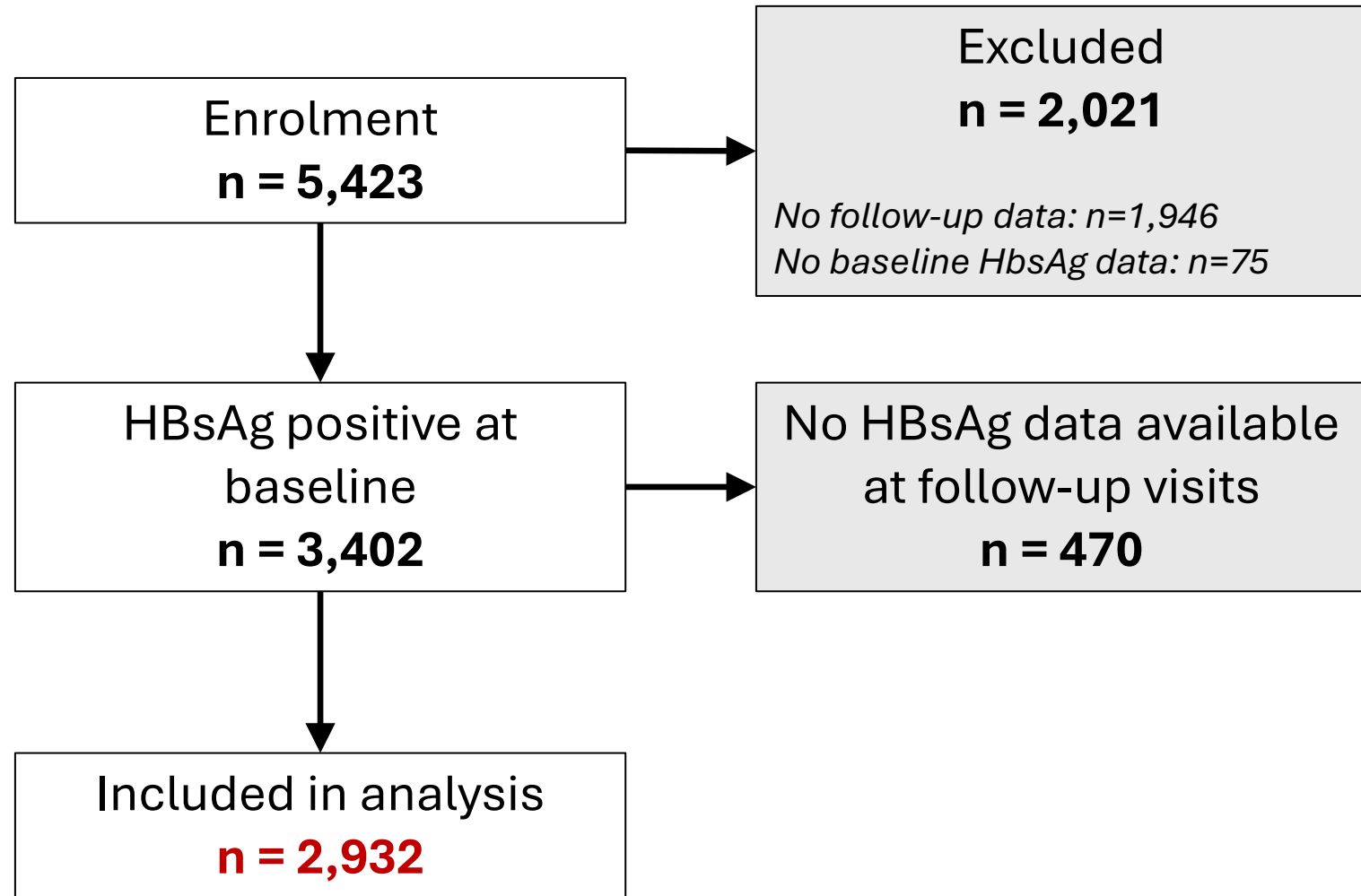
Definitions:

HBsAg loss: A negative HBsAg following a previously positive test.

Functional cure: Sustained HBsAg negativity for ≥ 6 months.



Results: Participants flow

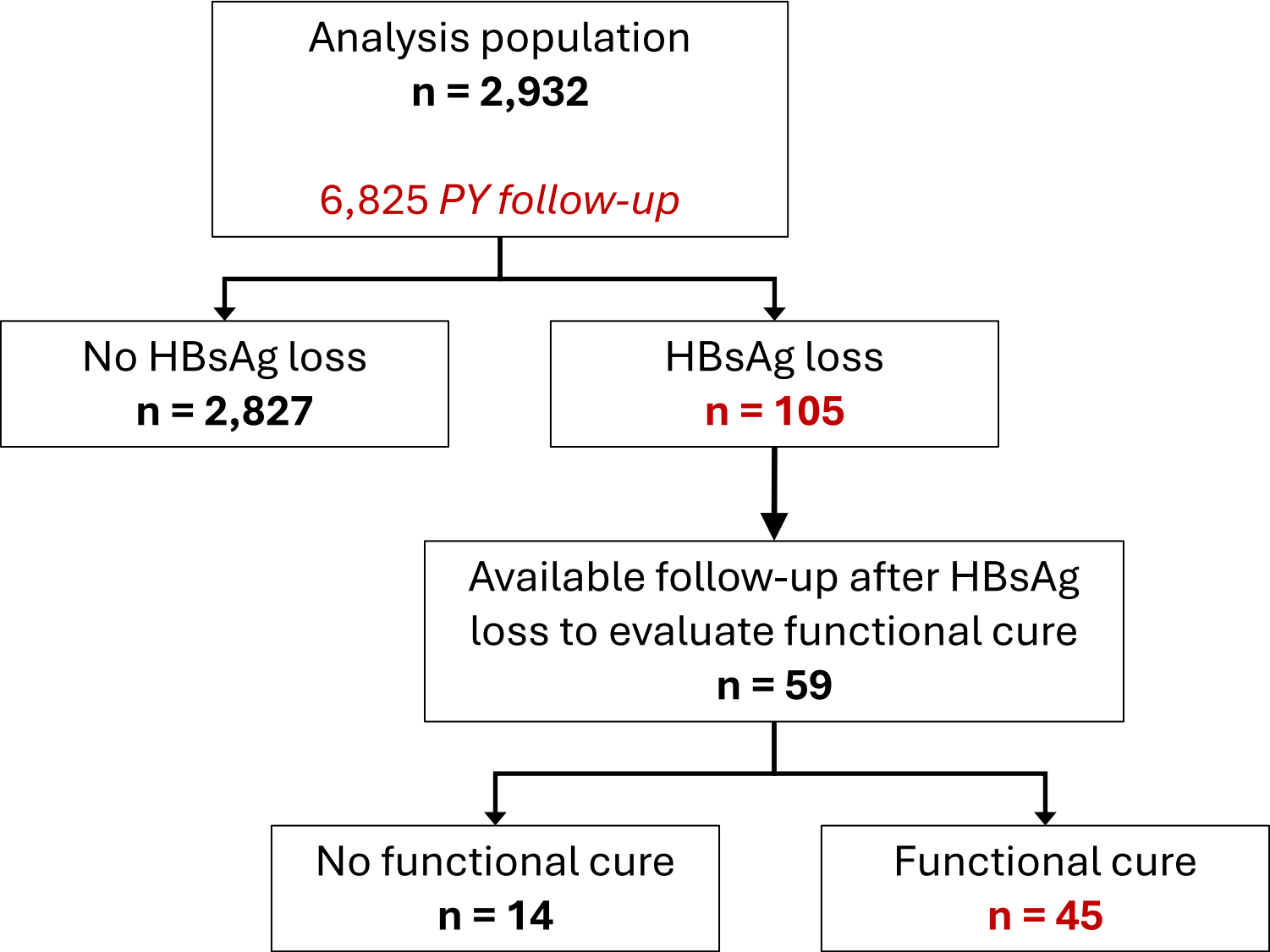


Results: Baseline characteristics

Baseline characteristics	n=2,932
Female	1323 (45%)
Median age (IQR), yr	47 (39, 59)
First Nations People	977 (33%)
Region of birth	
Australia	1087 (37%)
East/South-East Asia	1364 (47%)
Other	474 (16%)
Not available	7 (<1%)
Median time since HBV diagnosis (IQR), yr	12 (6, 21)
HBV clinical management	
Initial assessment	88 (3%)
Monitoring only	1473 (50%)
Antiviral treatment	1357 (46%)
Other	14 (1%)

Baseline characteristics	n=2,932
Cirrhosis	
No	2668 (91%)
Yes	186 (6%)
Not available	78 (3%)
HBeAg positive	
Negative	2267 (77%)
Positive	437 (15%)
Not available	228 (8%)
HBV DNA	
Undetected	768 (26%)
Detected not quantifiable, <20 IU/mL	653 (22%)
Detected quantifiable, 20-180M IU/mL	1300 (44%)
Detected, >180M IU/mL	67 (2%)
Not available	144 (5%)
Elevated ALT (F>19, M>30)	
No	1217 (42%)
Yes	1697 (58%)
Not available	18 (1%)

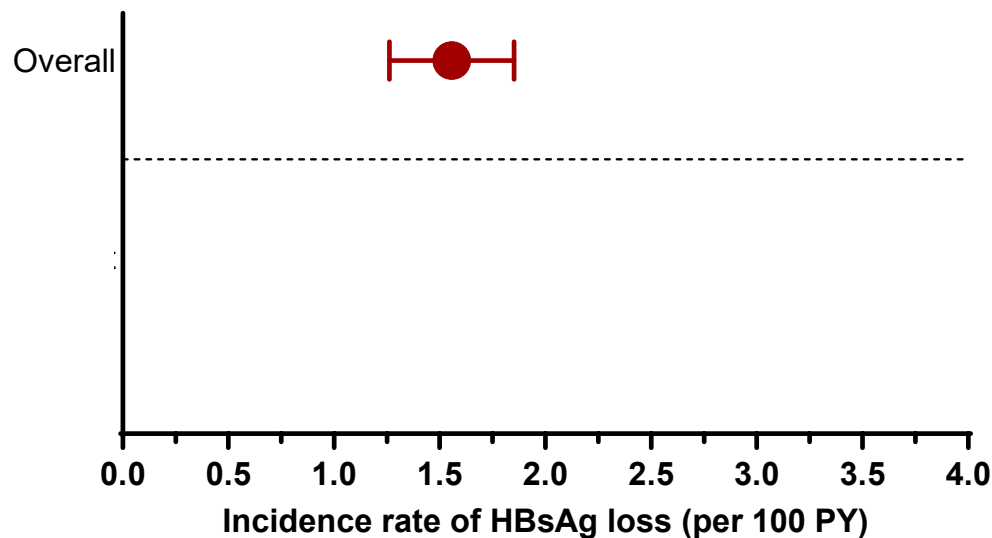
Results: Follow-up



Number of HBsAg tests per person	
2	934 (32%)
3	672 (23%)
4	281 (10%)
5	294 (10%)
6	286 (10%)
7	264 (9%)
8 or more	201 (7%)

	Follow-up	Testing interval
Median	2.2 yr	6.8 mo
IQR	1.3, 3.2 yr	5.9, 12.0 mo

Results: Incidence rate of HBsAg loss

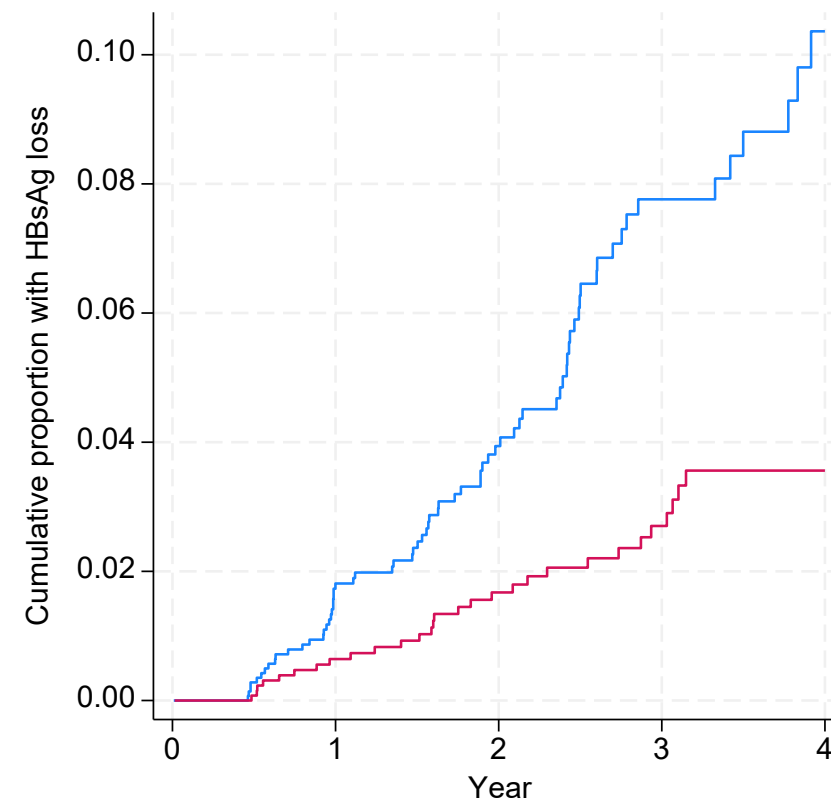


Overall rate: 1.5 per 100PY

95%CI: 1.3, 1.9 per 100 PY

Individuals under monitoring only: **2.2** per 100PY (**1.8, 2.8**)

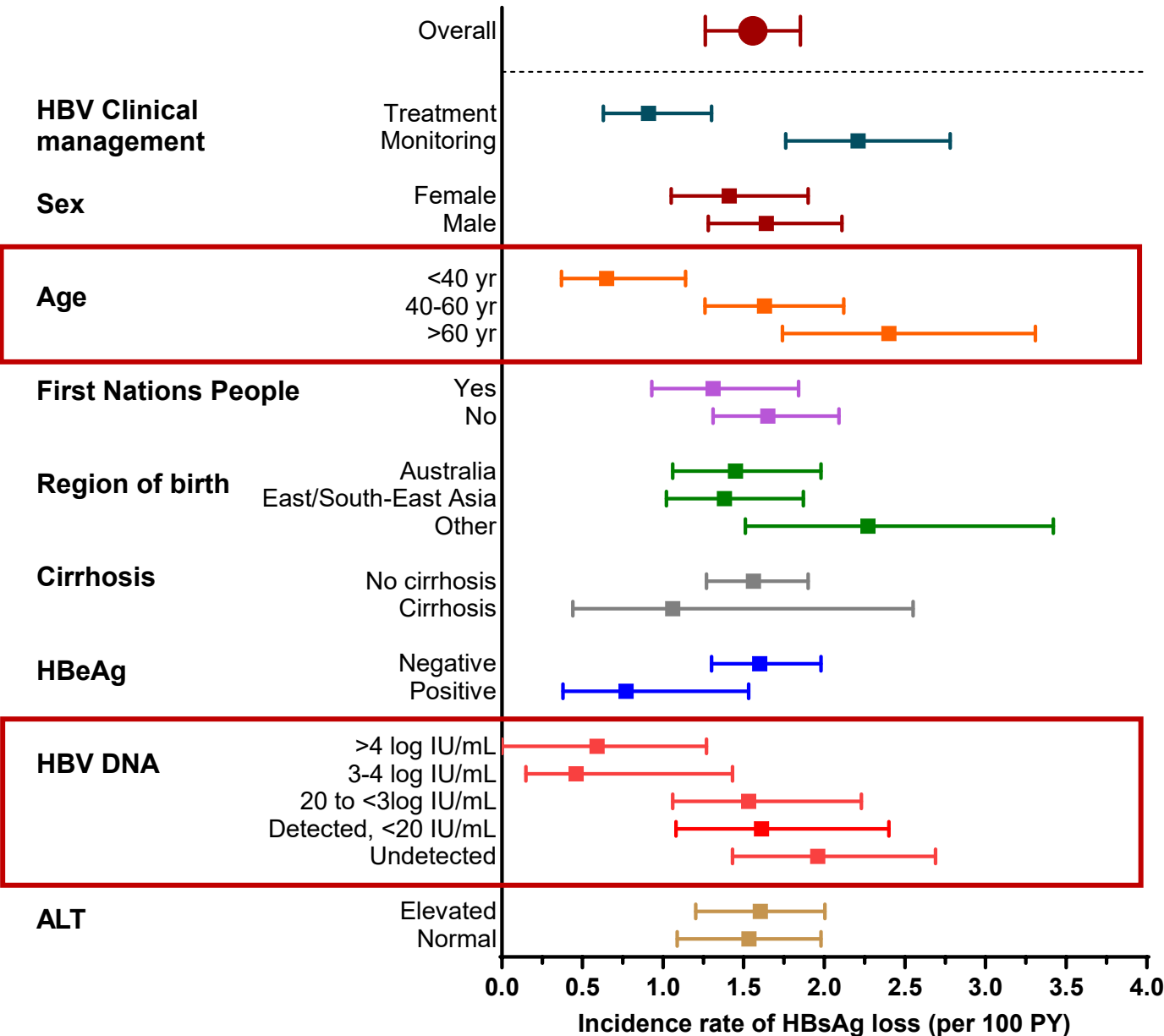
Individuals receiving treatment: **0.9** per 100PY (**0.6, 1.3**)



-- Monitoring only

-- Received treatment

Results: Incidence rate of HBsAg loss



Overall rate:
1.5 per 100PY
95%CI: 1.3, 1.9 per 100 PY

Note:
Variables not included given high missing values:

- HIV
- HDV
- Liver fibrosis stage

Results: Factors associated with HBsAg loss

	Adjusted HR (95%CI)	P
Age, yr	1.04 (1.02, 1.06)	<0.001
Female (vs. Male)	0.65 (0.41, 1.03)	0.065
First Nations People (vs. Non-Indigenous)	0.71 (0.18, 2.88)	0.633
Region of birth (vs. Australia)		
East/South-East Asia	1.59 (0.40, 6.35)	0.511
Other	2.28 (0.55, 9.44)	0.254
Receiving antiviral treatment (vs. Monitoring only)	0.11 (0.06, 0.22)	<0.001
Cirrhosis (vs. No cirrhosis)	0.78 (0.27, 2.24)	0.645
HBeAg Positive (vs. Negative)	1.03 (0.40, 2.65)	0.942
HBV DNA (vs. Undetected)		
Detected <20 IU/mL	0.49 (0.27, 0.88)	0.017
20 IU/mL to <3log IU/mL	0.30 (0.16, 0.55)	<0.001
3-4 log IU/mL	0.10 (0.03, 0.35)	<0.001
>4 log IU/mL	0.05 (0.01, 0.39)	0.004
Elevated ALT (vs. Normal)	1.31 (0.84, 2.06)	0.236

Note:

Baseline values of clinical data were used in the model (time-varying data of several variables not available for this analysis)

Some confounders for treatment (e.g., liver fibrosis stage, HIV, HDV) not included.

Results: Functional cure

Of **59** participants with HBsAg loss and Available follow-up after HBsAg loss,
45 achieved functional cure

Overall rate: 0.7 per 100PY; 95%CI: 0.5, 0.9 per 100 PY

Factors associated with functional cure in adjusted analysis

	Adjusted HR (95%CI)	P
Age, yr	1.03 (0.01, 1.07)	0.035
Receiving antiviral treatment (vs. Monitoring only)	0.07 (0.03, 0.18)	<0.001
HBV DNA (vs. Undetected)		
Detected <20 IU/mL	0.15 (0.05, 0.44)	0.001
20 IU/mL to <3log IU/mL	0.16 (0.07, 0.39)	<0.001
3 log IU/mL or higher	0.03 (0.00, 0.26)	0.001

Conclusion

- Among REACH-B participants, the annual **rate of HBsAg loss was 1.5% (1.3-1.9%)**, consistent with international estimates:
 - *Zhou, et al. Lancet Gastro & Hepatol 2019 (meta-analysis): 1.17% (0.94-1.41%)*
 - *Yeo, Gastroenterology 2019 (meta-analysis): 1.02% (0.79-1.27%)*
- The rate was **lower among participants receiving treatment**. This difference should not necessarily be interpreted as an effect of antiviral treatment itself. Treatment initiation is influenced by the phase of HBV infection, including viral replication, ALT levels, and liver fibrosis. The lower rate observed among treated participants may partly **reflect confounding by indication**.
- The rate was also **higher among older participants and those with lower HBV DNA levels** at baseline, consistent with the natural history of chronic HBV infection.
- Low viral replication is a key characteristic of the HBeAg-negative chronic infection phase (*i.e.*, inactive phase), increasing the likelihood of HBsAg loss. Older age is a surrogate for longer infection duration, suggesting longer time for transition to the inactive phase.
- This analysis could be further improved by using clinical data as time-varying covariates, and evaluating HBsAg loss and functional cure across various phases of chronic HBV infection.