

HDV Where do we go with double reflex testing ?

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Disclosures : robertgish.com

**The success of HDV reflex testing has
been shown in**

NYC

Spain

England

France

.....

RECOMMENDATIONS AND RATIONALE – HDV testing - Who to test?

New recommendations

Universal testing approach

Serological testing for anti-HDV antibodies may be performed **for all individuals** who are HBsAg positive, as the preferred approach to scale up access to HDV diagnosis and linkage to care

(conditional recommendation, very-low-certainty evidence)

Narrative review

- No studies directly evaluated impact and cost-effectiveness of different anti-HDV testing approaches.
- Observational studies from high income settings **show poor testing uptake and case-finding based on risk-based approach**, and marked increase with laboratory-based universal anti-HDV testing
- **Effective case-finding crucial to implement preventative interventions** eg. enhanced HCC surveillance, and access new treatment options



Priority population testing approach

In settings in which a universal anti-HDV antibody testing approach is not feasible because laboratory capacity or other resources are limited, testing for anti-HDV may be given **priority in specific populations** of HBsAg-positive individuals:

- people born in **HDV-endemic** countries, regions and areas;
- people with **advanced liver disease**, those receiving hepB treatment; and those with features suggesting HDV infection (such as low HBV DNA with high ALT levels); and
- people considered to have **increased risk** of HDV infection (haemodialysis recipients, people living with HCV or HIV, people who inject drugs, sex workers and men who have sex with men).

(conditional recommendation, very-low-certainty evidence)

RECOMMENDATIONS – HDV testing

How to test?

Diagnostic pathway

People with CHB (HBsAg positive) may be diagnosed with hepatitis D by using a serological assay to detect total anti-HDV followed by an NAT to detect HDV RNA and active (viraemic) infection among those who are anti-HDV positive.

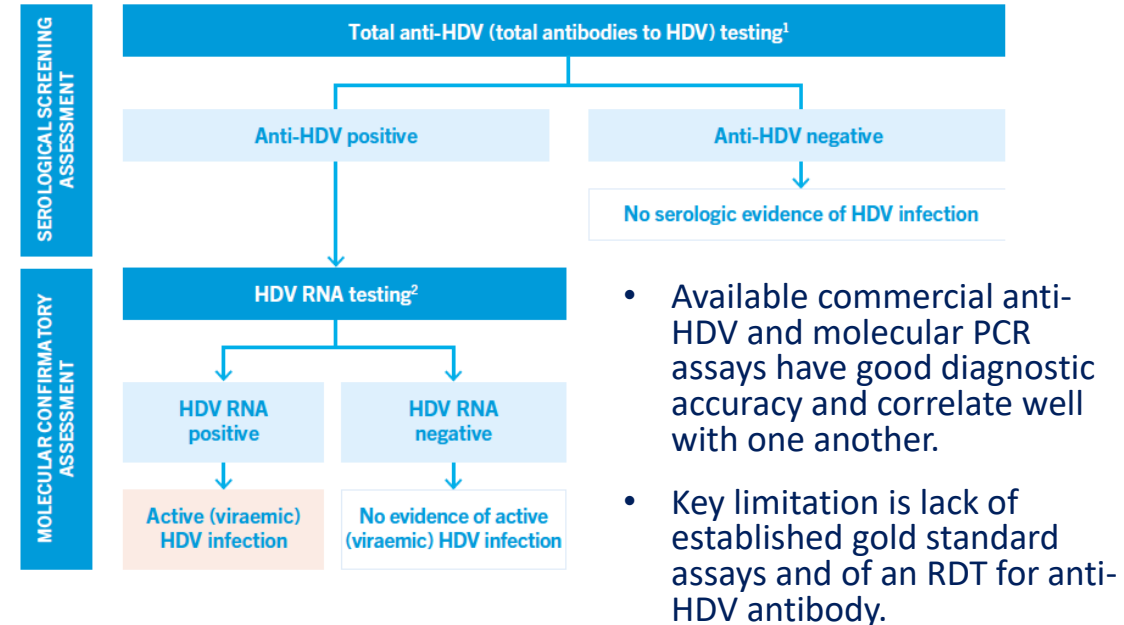
Assays should meet minimum quality, safety and performance standards.

(conditional recommendation, low-certainty evidence)

Reflex testing

Reflex testing for anti-HDV antibody testing following a positive HBsAg test result and also for HDV RNA testing (where available) following a positive anti-HDV antibody test result, may be used as an additional strategy to promote diagnosis.

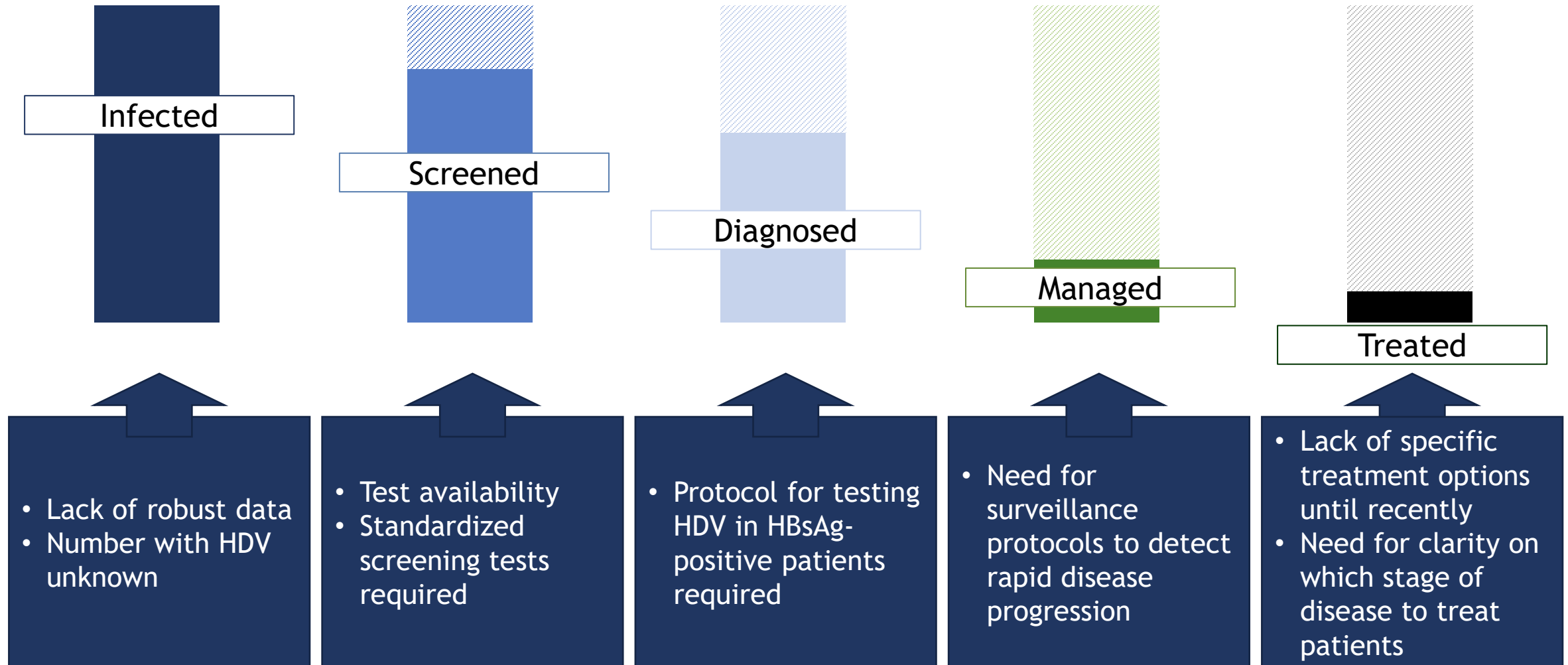
(conditional recommendation, low-certainty evidence)



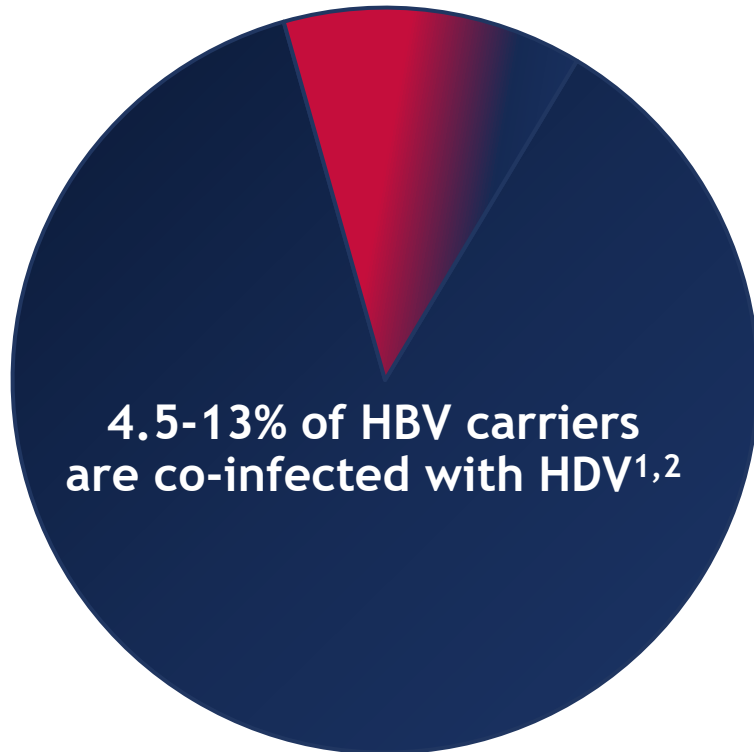
Systematic review of reflex testing

- 11 studies of reflex anti-HDV Ab testing (3 had non-reflex comparator arm) in those HBsAg positive
- Increased uptake of serology testing (97% (95% CI: 92–100%) vs. 45% (95% CI: 0.3–98%) vs. non-reflex testing
- Very high uptake of reflex HDV RNA in those anti-HDV positive - 98% (95% CI: 77–100%) in 8 studies.

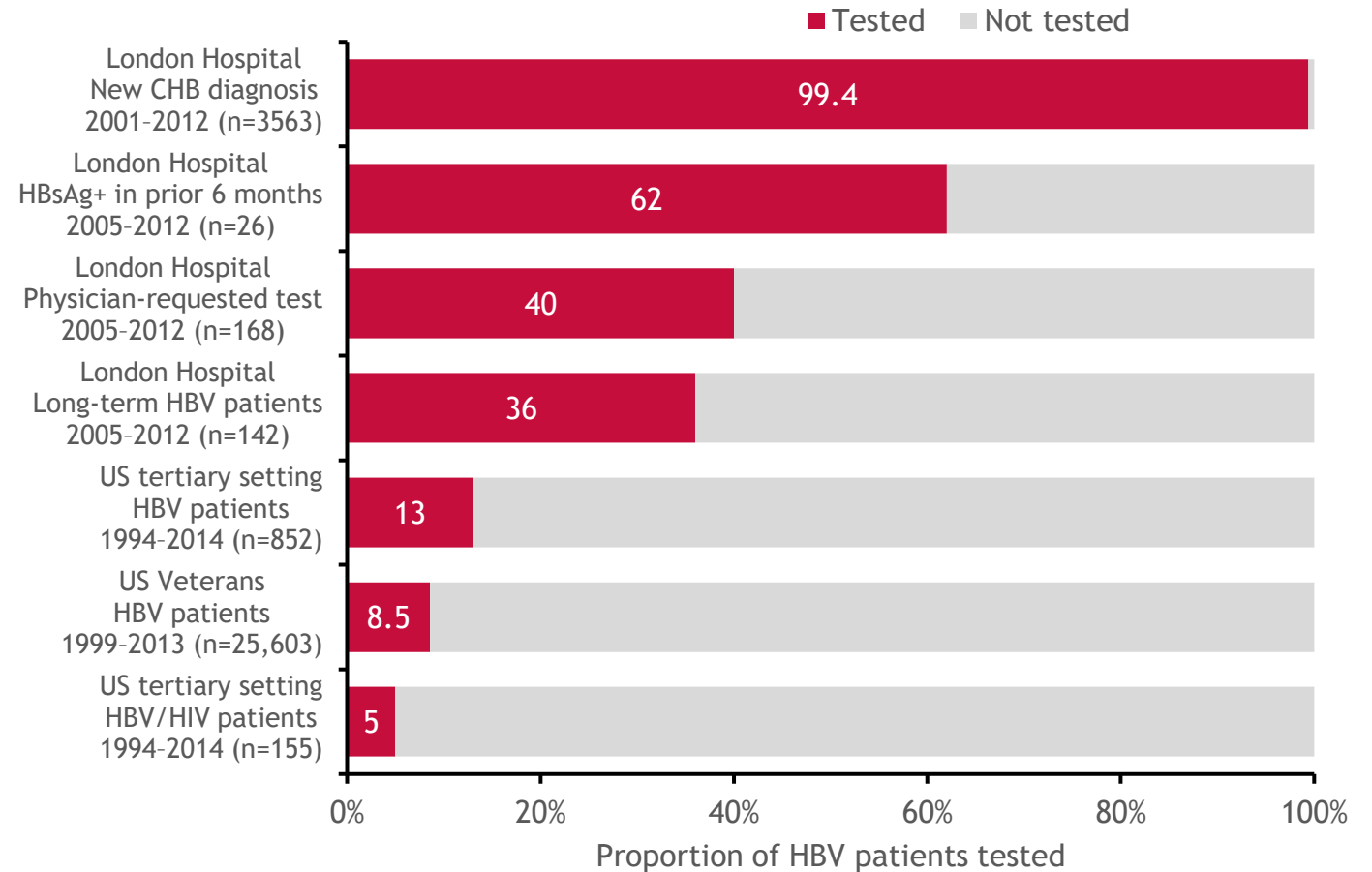
There are Unmet Needs Across the HDV Care Cascade



HDV Screening Occurs Inconsistently in HBV Patients Despite the Known Risk of Co-infection/Superinfection



HDV testing in HBV patients³⁻⁵



1. Miao Z, et al. J Infect Dis 2020;221:1677-87; 2. Stockdale AJ, et al. J Hepatol 2020;73:523-3;
3. Safaie P, et al. Virus Res 2018;250:114-7; 4. Kushner T, et al. J Hepatol 2015;63:586-92;
5. Bouzidi KE, et al. J Clin Virol 2015;66:33-7.

CHB: chronic hepatitis B virus; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus;
HDV: hepatitis D virus; HIV: human immunodeficiency virus.

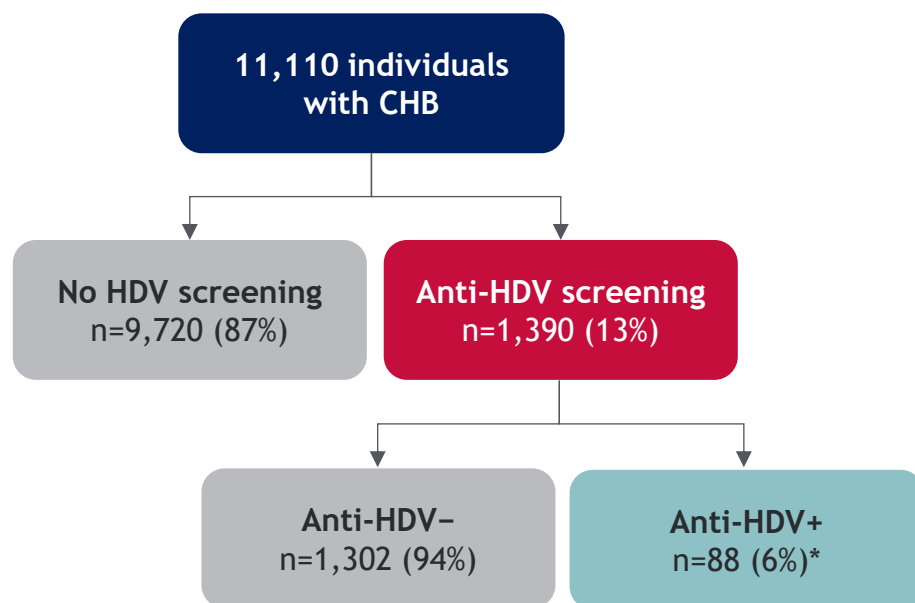




HDV Screening and Disease Burden in a US Center

Retrospective analysis evaluating screening patterns, patient characteristics and outcomes in HDV from January 2016 to October 2021

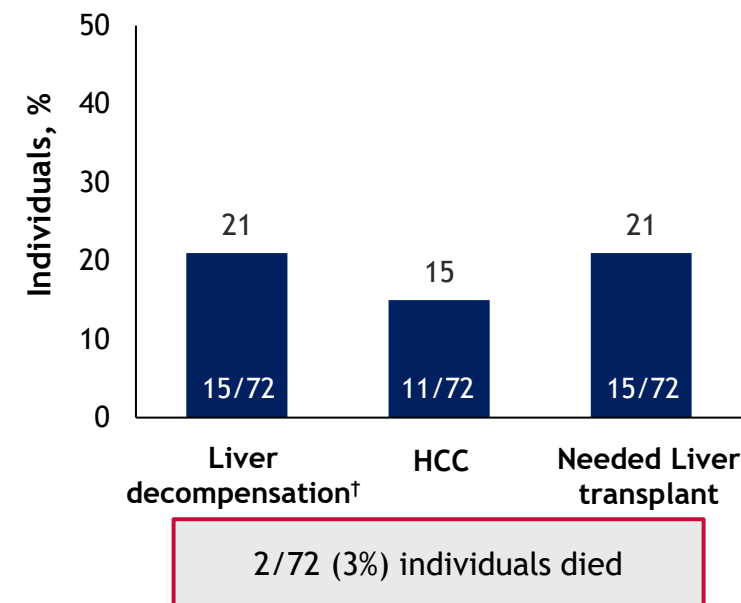
HDV Screening Patterns



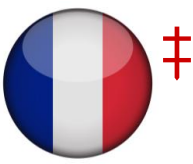
Anti-HDV+ Individuals

Characteristics at Time of Anti-HDV Testing	n=72
Age at diagnosis, mean	48
Male, n (%)	45 (63)
Cirrhosis, n (%)	40 (56)
Comorbidities, %	
HCV	11
HIV	8
NAFLD	7

Liver-Related Events (2016-2021)

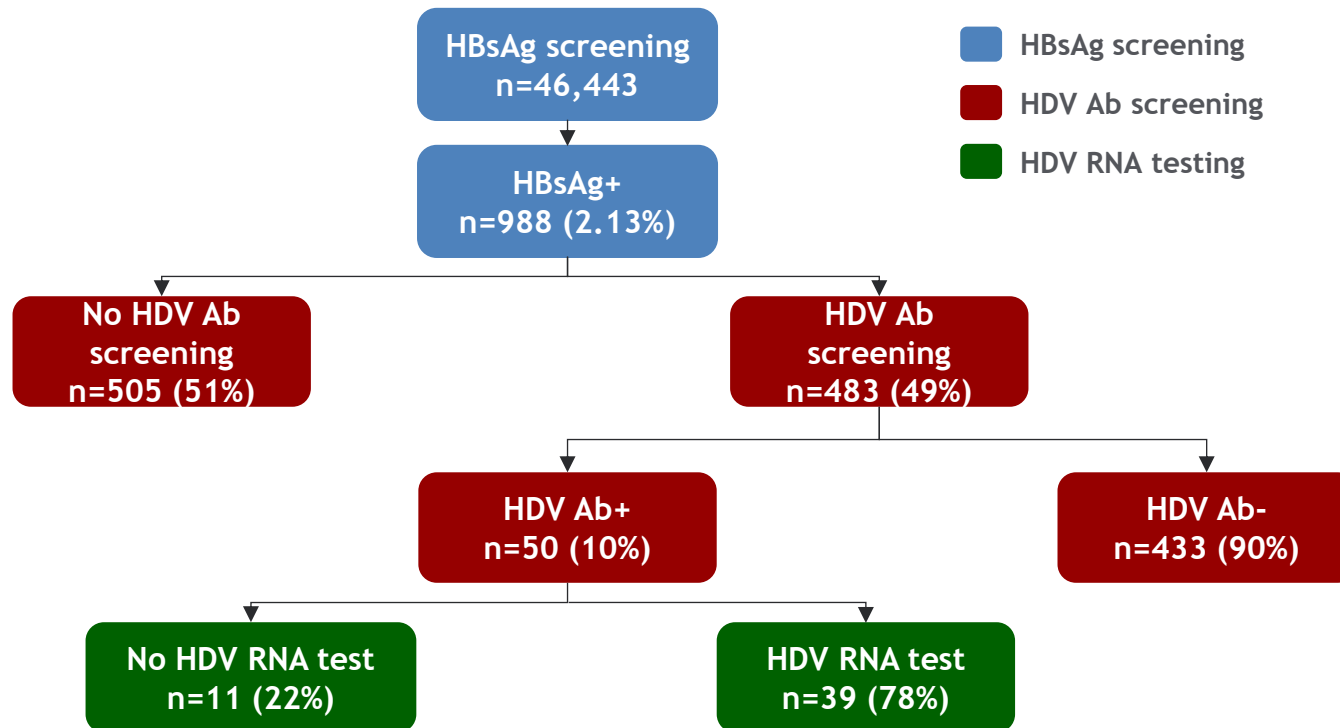


Despite high morbidity associated with HDV, only 13% of HBV were screened for HDV; universal screening for HDV among HBsAg carriers may be reasonable



HDV Screening at University Hospital of Bordeaux

Evaluation of the number of chronic HBV individuals with available HDV screening and HDV RNA testing from October 2018 to May 2021



Screening for HDV is suboptimal in a viral hepatitis expert center

51% of HBsAg+ patients were not screened for HDV Ab

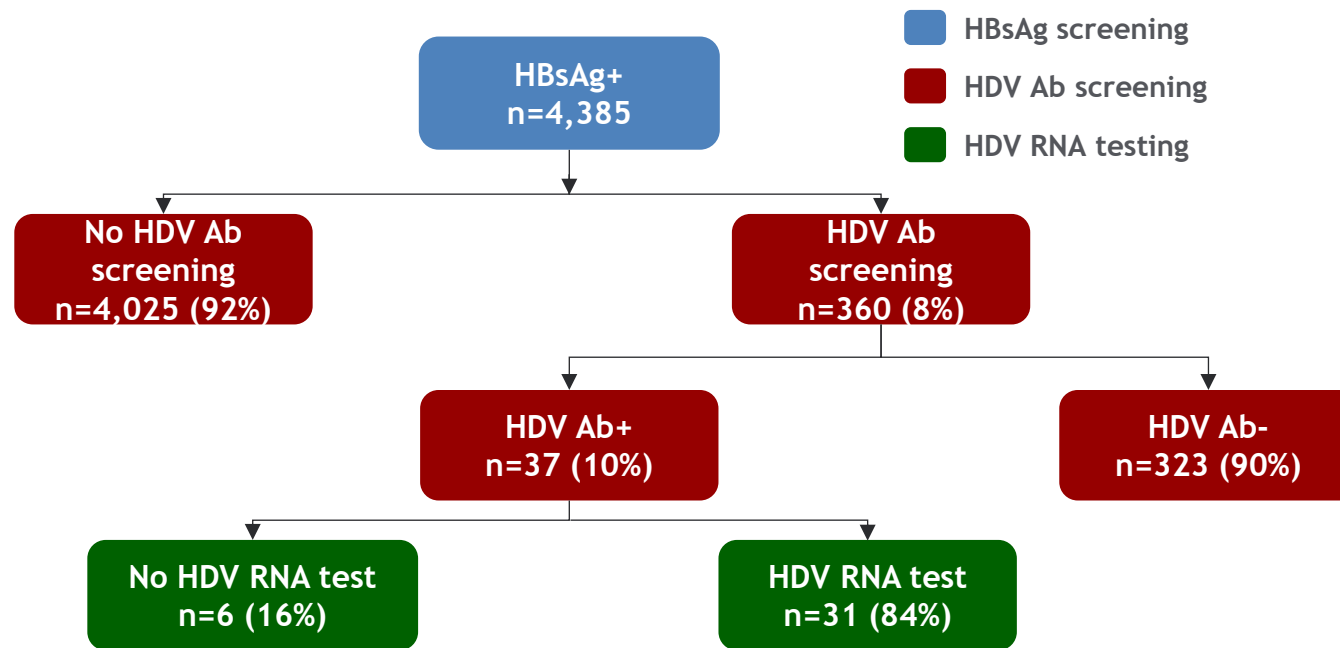
Health policy initiatives are needed to improve HDV screening and include reflex testing



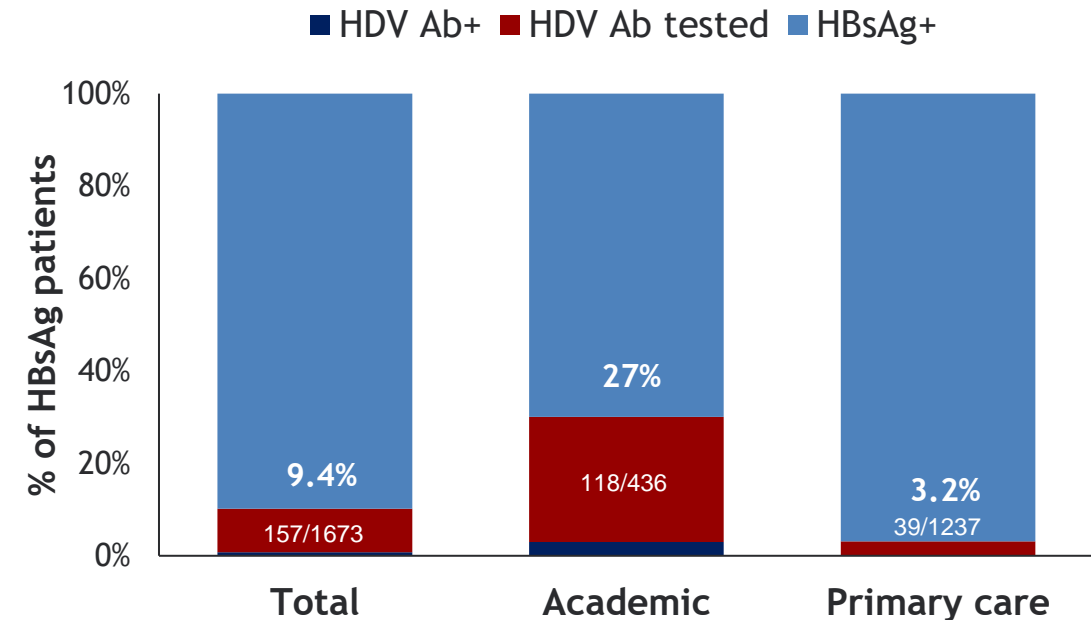
Screening of HDV in HBsAg+ Patients in Barcelona - Are EASL Guidelines Implemented?

Retrospective analysis of HBsAg+ serum samples from a central laboratory in January 2015 to May 2021

HDV Screening Cascade



HDV Ab Screening in Academic and Primary Care Post EASL Guidelines 2017



Despite guidelines being in place, a large proportion of HBsAg+ individuals remains untested for HDV.
New strategies and education on reflex testing should be considered

*1457 (33%) and 2929 (67%) of HBsAg+ samples came from academic hospitals and primary care centers respectively
282 (78%) and 78 (22%) of anti-HDV requests came from academic hospitals and primary care centers, respectively
EASL guidelines recommendations for HDV screening did not differ pre-2017.
Palom A, et al. AASLD 2021. Oral 224



Challenges and Potential Solutions to Screening



Challenges



HDV endemicity remains unclear due to limited studies and inconsistent reporting in populations of CHB patients.^{1,2}



Recommendations for risk-based screening fail to identify patients due to poor clinician awareness of risk groups.²



Poor clinician and patient awareness of HDV screening, diagnosis and prevention.^{2,3}



Barriers to care in high-risk populations exist, including access to doctors.³



Screening guidance recommendations vary and are based on provider discretion.⁴⁻⁷



Reliability of laboratory derived tests (LDTs) vary between tests and across genotypes.⁸⁻¹⁰

Potential Solutions



- **Universally screen all HBsAg⁺ patients.**
- Include routine HBV testing on the US immigration medical exam.



- Include hepatitis delta as a disease reportable to the CDC.



- Provide educational initiatives for provider awareness, as well as targeted, patient-centered education on hepatitis delta.



- Increase access to HBV vaccinations, testing, and care.



- Develop HDV-specific screening guidelines.
- **Implement anti-HDV reflex testing.**



- Evaluate the appropriate LLoD for HDV RNA assays.
- Design HDV RNA tests with sensitivity to non-HDV-1 genotypes.

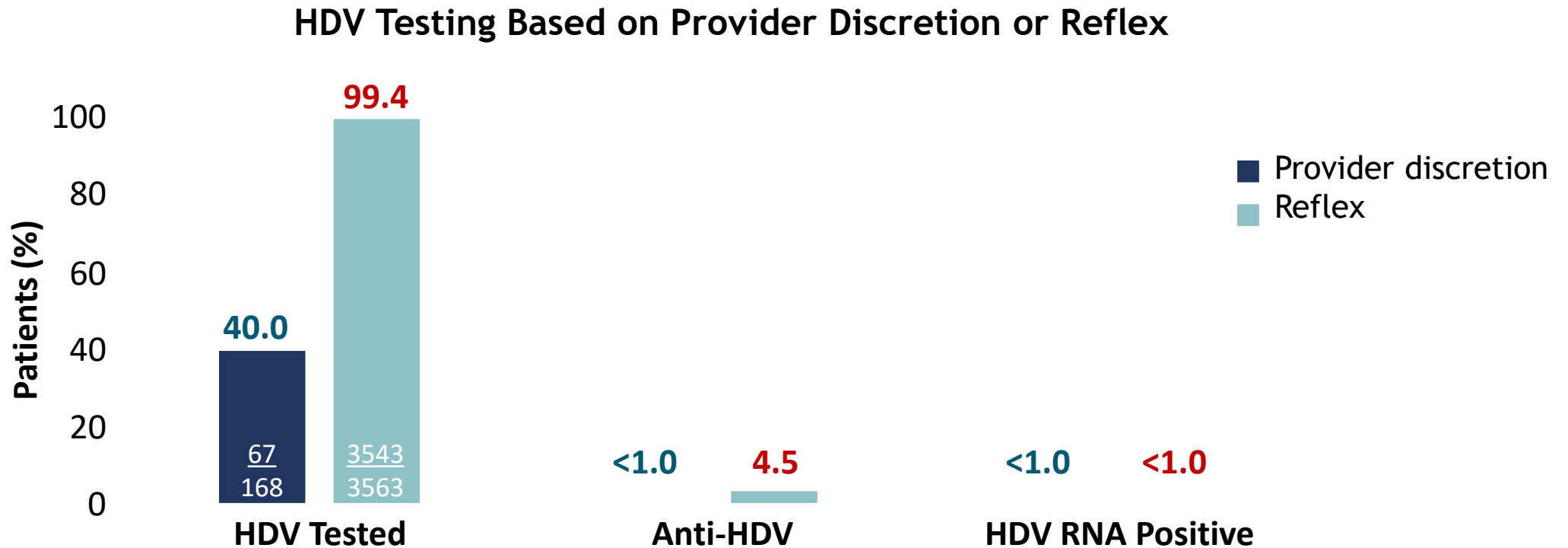
Due to underreporting of HDV, poor clinician awareness, and challenges in screening for hepatitis delta, solutions such as universal testing of HBsAg⁺ patients and anti-HDV reflex testing have been proposed.





HBsAg-Positive Reflex to Anti-HDV

- Cross-sectional analysis of HDV testing among HBsAg-positive patients at 2 London Centers, 2005-2012



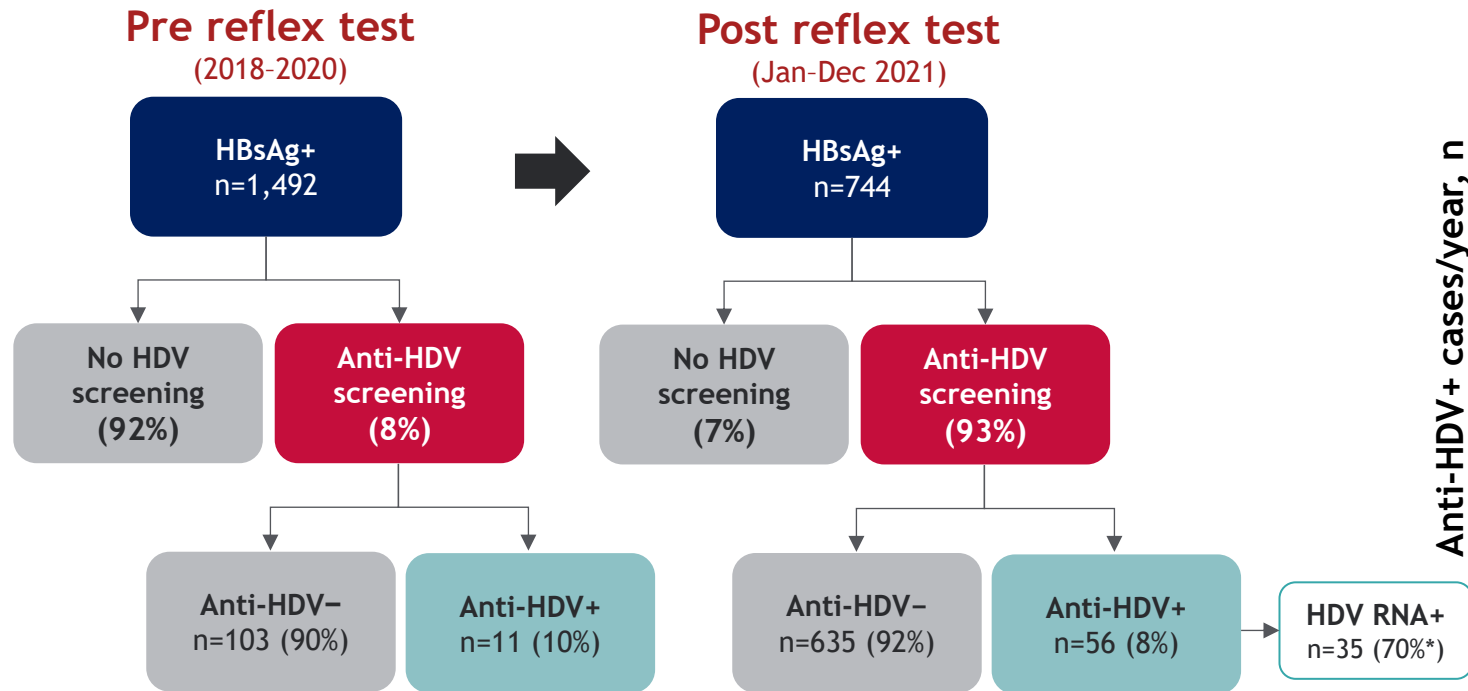
- Center with a reflex laboratory algorithm achieved anti-HDV testing of almost all first HBsAg-positive samples over a 12-yr period



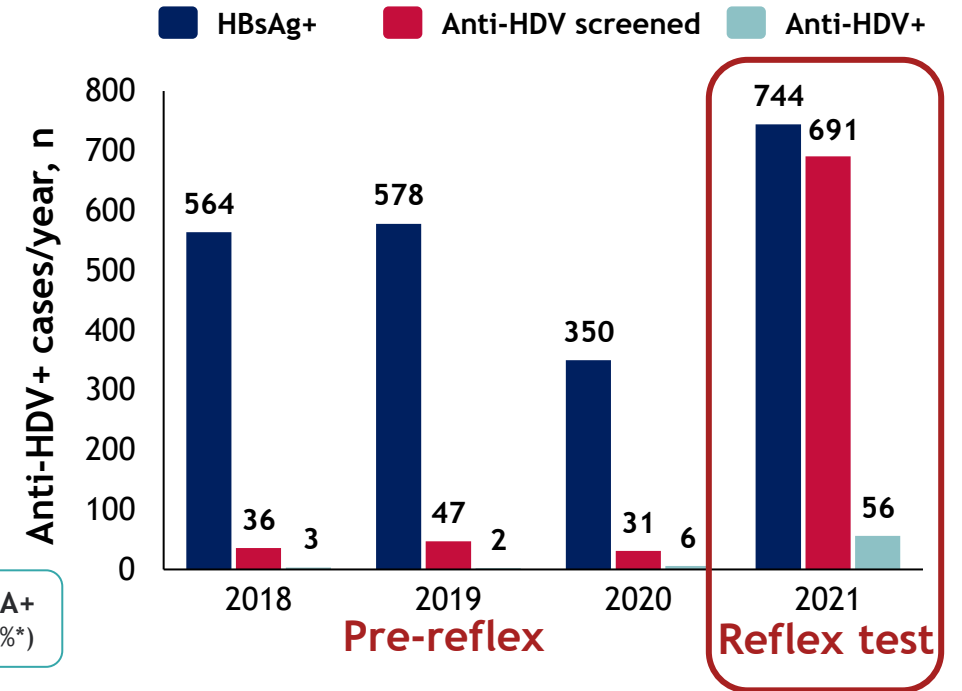
Implementation of HDV Reflex Testing in HBsAg+ Patients

Analysis of HBsAg+ samples before and after anti-HDV reflex test implementation in an academic hospital and 17 primary care centers

HDV Screening Cascade¹



Anti-HDV+ Cases Detected²



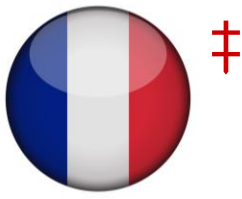
Implementation of anti-HDV reflex testing led to a marked increase in the identification of anti-HDV+ individuals

*HDV RNA evaluated in 50 anti-HDV+ individuals

HBsAg, hepatitis B surface antigen.

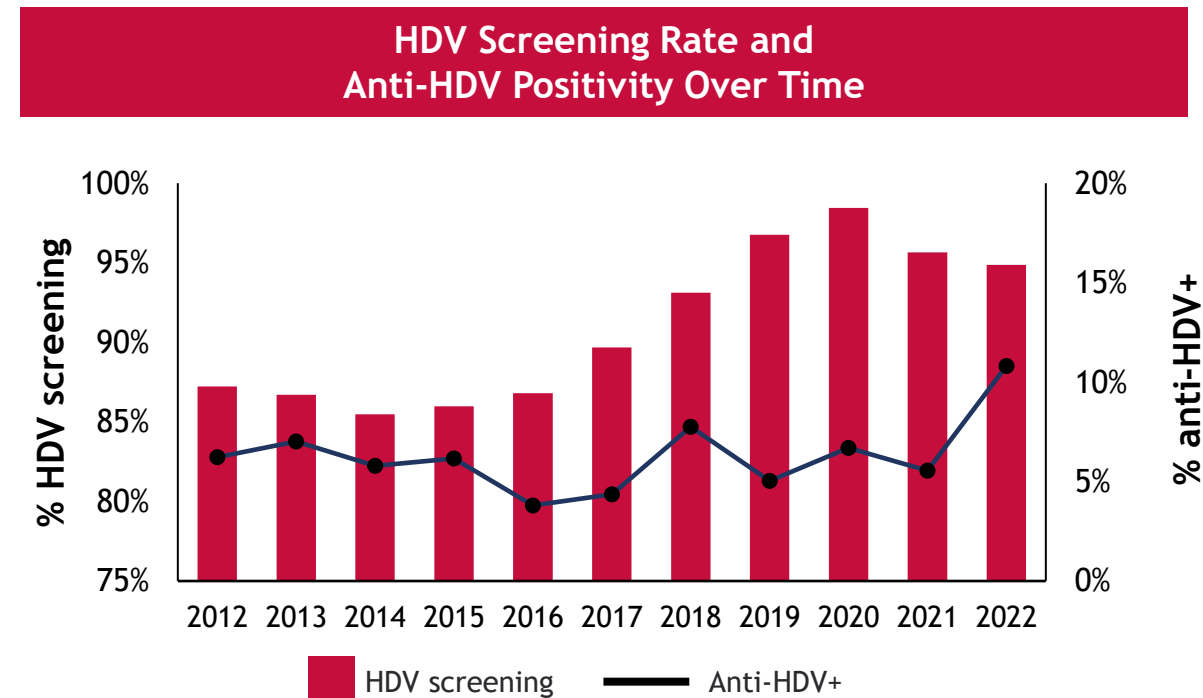
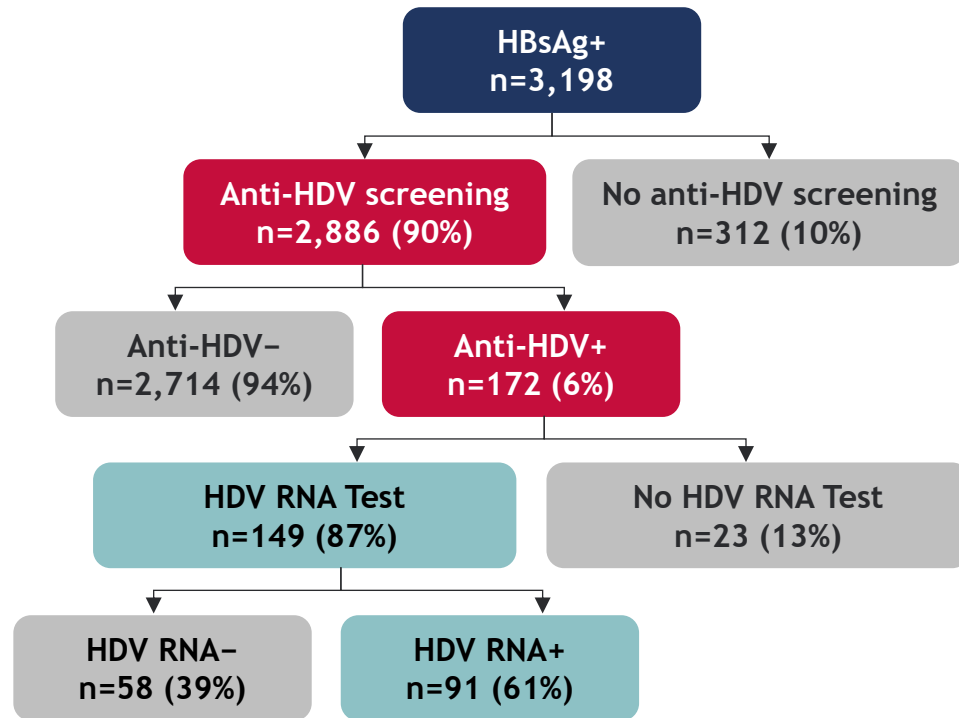
1. Palom A, et al. EASL 2022. Poster #THU367; 2. Palom A, et al. AEEH 2022. Poster #P076





HDV Reflex Testing Program Outcome in France

Single-center, retrospective survey of an anti-HDV reflex testing protocol over 10 years (2012-2022)



Reflex testing led to an increase in HDV screening rates over time, and exceeds 90% from 2018 onwards





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Hepatitis Delta Virus (HDV) is a severe co-infection in patients with Hepatitis B Virus (HBV), associated with worsened outcomes and increased risk of liver disease progression.¹ However, screening for HDV remains alarmingly low in the United States, with studies reporting that fewer than 20% of HBV patients are tested for HDV co-infection.^{1,2} This low screening rate may in part be due to the current guidelines from the American Association for the Study of Liver Disease (AASLD), which recommend HDV testing only for HBV patients with specific risk factors.³ As a result, HDV prevalence may be significantly underestimated, delaying diagnosis and access to treatment for many patients.

The primary objective of this study is to evaluate the effectiveness of automatic reflex HDV (AR-HDV) testing in increasing the detection of HDV co-infections among HBV-positive patients in the University of Utah UHealth system. Prior studies have indicated that reflex testing, where HDV tests are automatically ordered for all HBV-positive patients, significantly increases the identification of HDV co-infections, particularly among individuals who may not meet traditional risk-based guidelines.⁴ Our study includes a direct comparison between provider-driven testing practices and reflex HDV testing to assess key metrics related to screening and detection rates.

Persons born in regions with noted high HIV prevalence

- Africa (West Africa, West of Zairian, Asia (Central and South Asia), Vietnam, Afghanistan, Pakistan, Japan, Taiwan), Pacific Islands (Kiribati, Nauru), Middle East, Eastern Europe (Southern Kazakhstan, Kyrgyz), South America (Venezuela, Colombia, Chile)

Men who have sex with men (MSM)

Persons with history of STDs

Persons with HIV (+) or HIV(-) individuals

Persons with multiple sexual partners or history of STI

Elevated ALT or AST with low or undetectable HIV RNA

Recommendations for HIV Testing:
 Ask +HIV antibody, if positive, HIV RNA

Terrault et al. 20108

Figure 1. Current AASLD Guidelines for HDV Testing. This figure outlines the current testing recommendations for HDV as per the AASLD guidelines.³

HBV and HDV Testing Performed



Figure 2. Study Overview of HBsAg-Positive Patient Plasma Collection and Testing Process. This figure provides an overview of

Table 1. Demographics of HBSAg(+) Cohort

	HBSAg(+) n = 201
Sex	
Male	109 (54.22%)
Female	92 (45.87%)
Age	
Average Age \pm SD	46.40 \pm 14.88
Age Groups	
<20	4 (1.99%)
20-29	21 (10.45%)
30-39	48 (23.88%)
40-49	47 (23.38%)
50-59	35 (17.41%)
60-69	31 (15.43%)
70-79	13 (6.47%)
80+	2 (0.99%)

Race	
AIAN	2 (1.5%)
Asian	80 (39.80%)
Black	42 (21.00%)
NHPI	10 (4.98%)
White	43 (21.40%)
Unknown	23 (11.44%)

Ethnicity	
Hispanic/Latino	8 (3.98%)
Not Hispanic/Latino	164 (81.60%)
Unknown	29 (14.43%)

HBV Status	
Acute	32 (15.92%)
Chronic	169 (84.08%)

American Indian/Alaska Native (AIAN)
Native Hawaiian/Pacific Islander (NHPI)

Table 2. Testing Profile in HDV Provider and Reflex Tested Cohorts

	HBV Cohort n = 201	Acute HBV n = 32	Chronic HBV n = 169
HDV Testing (Provider)			
Prior HDV Testing Performed	117 (58.21%)	14 (43.75%)	117 (69.23%)
Prior HDV(+) Status	11 (5.47%)	2 (6.25%)	9 (5.33%)
HDV Testing (Reflex Cohort)			
Reflex HDV Testing Performed	201 (100%)	32 (100%)	169 (100%)
Reflex HDV(+) Status	11 (5.47%)	1 (3.13%)	10 (5.92%)

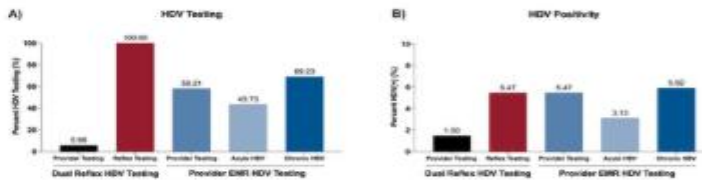


Figure 3. HDV testing and positivity rates. A) Provider-based HDV testing occurred in 5.98% of HBSAg(+) patients in the Dual Reflex HDV Testing Protocol, with 100% of the HBSAg(+) samples undergoing both HDV-Ab and HDV-PCR testing. The positivity rate of HDV-Ab testing was 38.21% of 165 samples undergoing HDV testing at some stage in their medical history. **B)** Provider-based HDV testing identified 1.50% HDV positivity, whereas Dual Reflex HDV Testing identified 5.47% of same samples tested positive for HDV-Ab and/or HDV-PCR. HDV positivity rate was 1.50% in provider testing and 5.48% with reflex HDV testing protocols. Analysis of EMR identified that 5.47% of HBV patients had a positive test for HDV at some stage in their medical history.

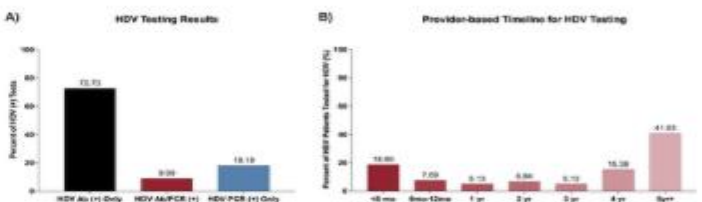
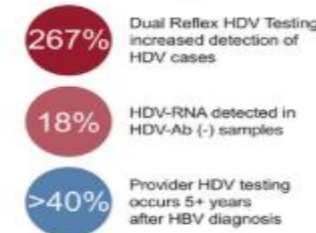


Figure 4. HIV testing type and timeline for provider-based HIV testing. A) Dual Reflex HIV testing as performed by the testing facility. The majority of sample testing was only positive for HIV Ab (53.64%), with 18.18% of sample testing positive for HIV PCR only, $n=201$. B) Analysis of the timeline between initial HIV diagnosis and HIV testing identified that >40% of HIV cohort was not tested for HIV until 5+ years after original HIV diagnosis. The second most tested timeframe was within 6 months of HIV diagnosis (18.80%), $n=117$.

A Venn diagram with two overlapping circles. The left circle is labeled 'Dual Reflex HDV Tested' and contains the value '36%'. The right circle is labeled 'Provider HDV Tested' and contains the value '36%'. The overlapping area in the center is labeled '64%'.

Figure 5. Dual Reflex HDV Testing detected 4/11 (36%) undiagnosed HDV coinfections. These cases were detected in the HBSAg(+) Chronic HBV cohort.



Significant deficiencies exist in HDV screening among HBV patients:

- There is a 266.67% increase in positivity rate in Dual Reflex HDV testing compared to provider initiated testing.
- A majority of HBsAg(+) tests were from Chronic HBV cohort (84.08%).
- >40% of the HBV cohort underwent HDV testing 5+ years after initial HBV diagnosis.
- Underdiagnosis of HDV due to limited testing may lead to untreated disease progression.
- Integrated and proactive management strategies are crucial to optimize outcomes for HBV and HDV co-infected patients.

REFERENCES

ACKNOWLEDGEMENTS



Implementation of HBsAg to HDV Ab Reflex Testing in a New York City Health System

Anna Mageras, Damodara Rao Mendu, Maria McGuire, Lauren Alpert,
Jimmy Wu, Kristie Heiden, Michael Fisher, Nina Rodriguez,
Cecilia Katzenstein, Andrea D. Branch, Douglas T. Dieterich,
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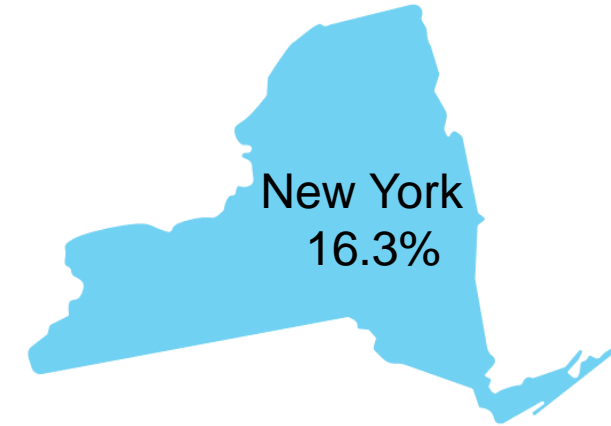
Disclosures

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Consulting/Ad Boards: Gilead, NOVO Nordisk, The Kinetix Group

Background

- Hepatitis Delta virus (HDV) is most severe form of viral hepatitis.¹
 - HDV requires hepatitis B virus (HBV) for replication.
- U.S. HDV Ab prevalence among HBsAg+ ~4.6–11.8%.^{2,3}
 - ~25% of U.S. HDV is in NYC Metro Area.³
- 2021–2023 in the Mount Sinai Health System (MSHS), only 54% of HBsAg+ patients received HDV Ab testing.⁶
- New HDV treatments on the horizon → need for better screening.



Prevalence of HDV among HBV population by U.S. state.²

1. Brunetto MR, et al., *Journal of Hepatology*, 2023.
2. Gish RG, et al., *Hepatology*, 2024.
3. Martins EB, et al., DDW 2017.
4. Alpert L, et al., EASL 2023.

Model Viral Hepatitis Screening Interventions

HBsAg +

HDV Ab

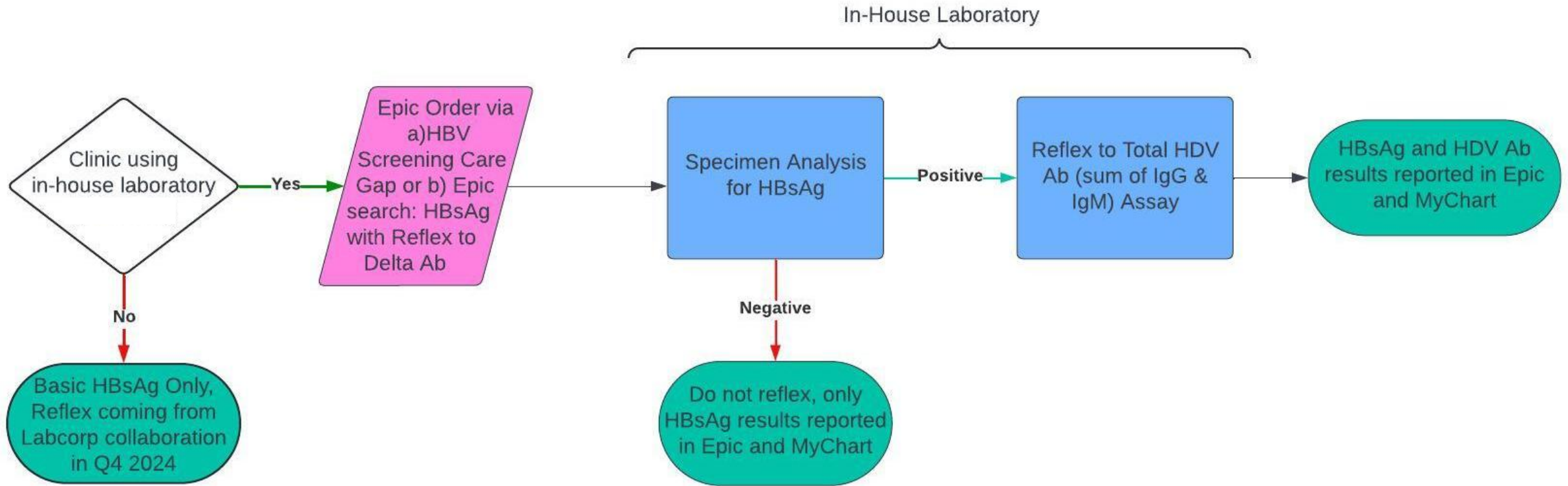
- A few health systems, mostly in Europe, have HBsAg+ to HDV Ab reflex testing.
 - HDV Ab screening rates increased from 8–35% at baseline to 64–100% with reflex.¹⁻⁴
- Our health system has prior experience with viral hepatitis screening programs:
 - Increased HCV RNA follow-up testing from 64% to 100% via reflex.
 - Increased HBV screening from 3% to ~20% via “Care Gap” prompt for primary care providers (PCPs) in EPIC electronic medical record (EMR).⁵

1. Palom A, et al., *JHEP Rep*, 2022.
2. Hilleret MN, et al., *JHEP Rep*, 2024.
3. Parfut A, et al., *J Clin Virol*, 2024.
4. Cossiga V, et al., *Liver International*, 2023.
5. Mageras A, et al., *EASL* 2023.

Aims

1. **Improve HDV Ab screening rates** among HBsAg+ patients in our large, urban, multicenter health system by implementing HBsAg to HDV Ab reflex testing.
2. **Evaluate impact** of reflex testing on HDV Ab screening rate.
3. **Provide a case study** to other health systems in the U.S. seeking to implement HBV to HDV reflex testing.

Reflex Test Logic Flow



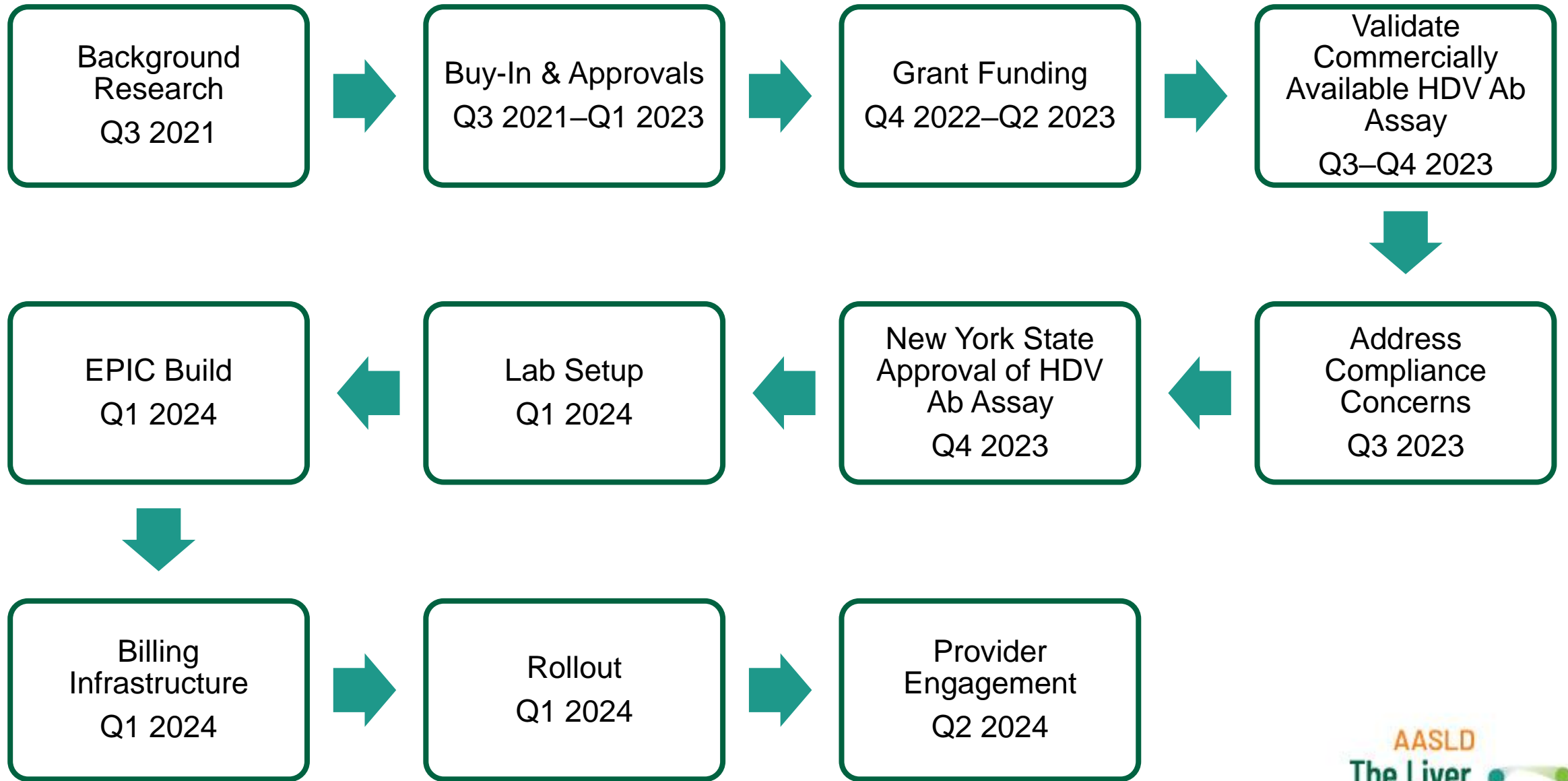
EPIC = electronic medical record used by most of MSHS

MyChart = online portal that makes test results directly available to patients

Challenges Encountered in Implementation Process

Challenge	Solution
No FDA-approved HDV Ab assay.	New York State approval.
No in-house HDV Ab test.	<ul style="list-style-type: none">• Validate commercially available Total HDV Ab IgG and IgM assay for in-house use.<ul style="list-style-type: none">• Assay method: Competitive enzyme immunoassay (ELISA).• Manufacturer: International Immuno-Diagnostics.
Compliance concerns about need for patient consent.	<ul style="list-style-type: none">• Test labelled as reflex; no surprise to provider or patient.• Option to order standalone HBsAg.• Involved HDV Community Advisory Board in decision.
“HEP B AG W/RFLX HEP D AB” order hard to find in EMR.	Add search terms in EPIC EMR.

Implementation Timeline of HDV Reflex Testing in MSHS



Ordering from the Care Gap Tab in EPIC EMR

CARE GAPS

Hepatitis B Screen

Depression Screening (PHQ2...

HIV SCREEN

Hepatitis C Screening

4 more care gaps

PROBLEM LIST

None

Hepatitis B Screen

Never done (Once)

Previous Completions

No completion history for this

View complete topic history

SmartSets

Associate

Edit Multiple

Patient Estimate

Providers

Select a pharmacy

Remove

Pend

Sign

OVERDUE/DUE SOON CARE GAPS

Manage User Versions

Hepatitis B Screen

Hepatitis B Screen

Hepatitis B Surface AB Qual

Normal, Routine

Release to MyMountSinai (MyChart)? Auto-release

HEP B AG W/RFLX HEP D AB

Hepatitis B Surface AG (HBSAG Screen) with Reflex to HDV AB

Normal, Routine

Release to MyMountSinai (MyChart)? Auto-release

Hepatitis B Core AB Total

Normal, Routine

Release to MyMountSinai (MyChart)? Auto-release

Need for hepatitis B screening test [Z11.59]

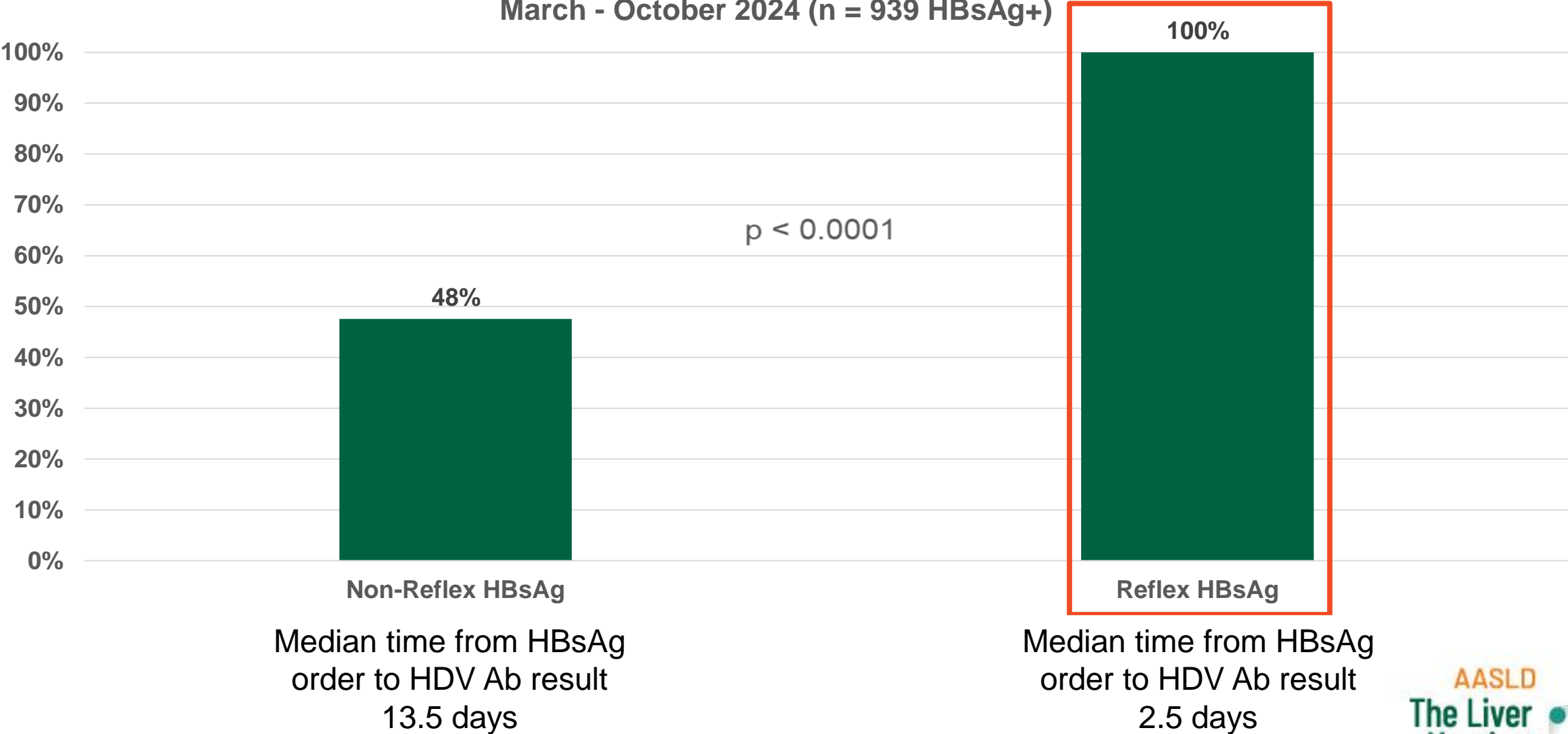
Provider Tip Sheet

Follow-Up Actions

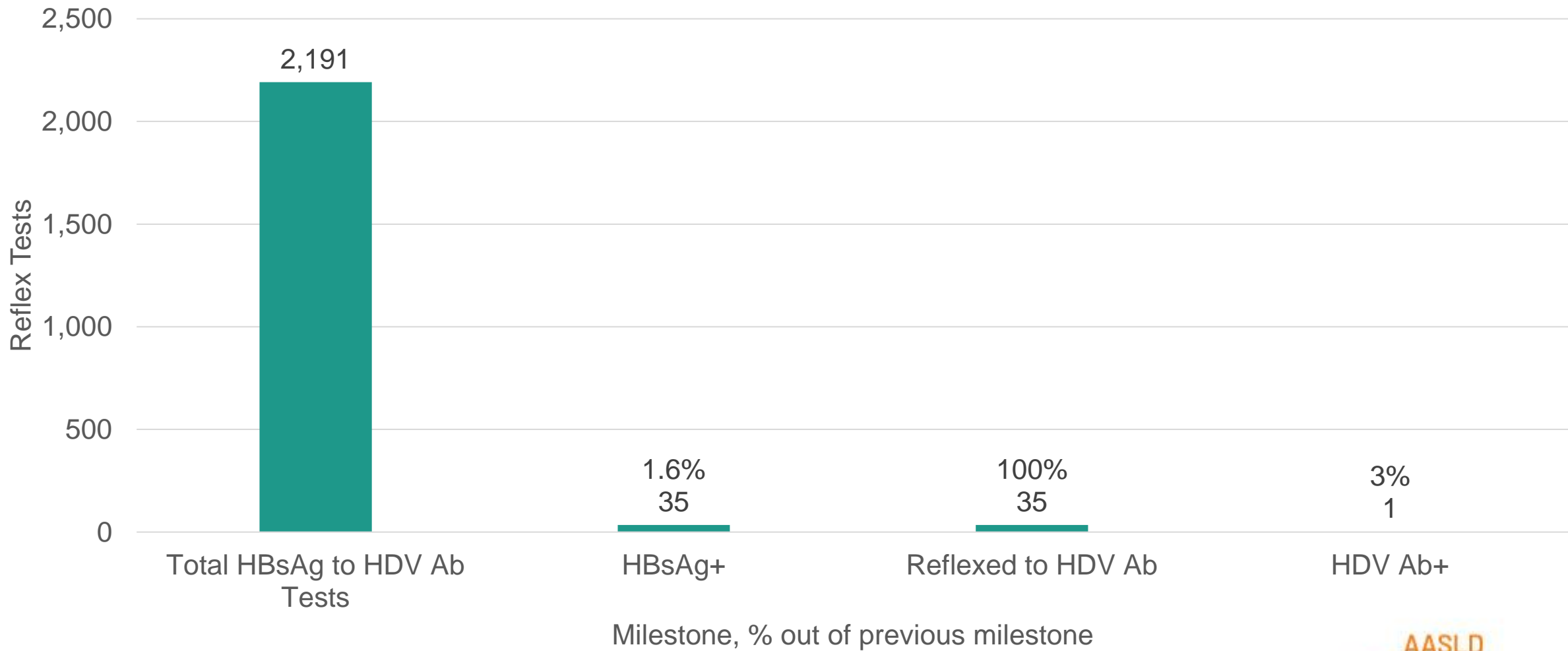
RESULTS	ACTION	MYCHART SMARTPHRASE FOR PATIENT EDUCATION
HBsAg+	Refer to LEAP Patient Navigation Team (AMB REF TO LEAP [56853]).	.HepBPositiveMyChart
	If HDV Ab+ , referral is particularly urgent due to aggressive nature of HDV.	.HepB+DPositiveMyChart
All Three Neg	Vaccinate with 2-dose Heplisav.	.HepBVaccinateMyChart
HBcAb+ HBsAg- HBsAb+/-	Counsel patient cleared a past HBV infection. If immunosuppression is needed, they are at risk for HBV reactivation. Recommend LIVER referral beforehand: 212-241-7270.	.HepBCoreMyChart
HBsAb+ HBsAg- HBcAb-	Reassure patient they are immune.	.HepBImmuneMyChart

HDV Ab Screening Rate Among HBsAg+ Unique Patients

HDV Ab Screening Rate (Ever Screened) after Reflex Implementation
March - October 2024 (n = 939 HBsAg+)

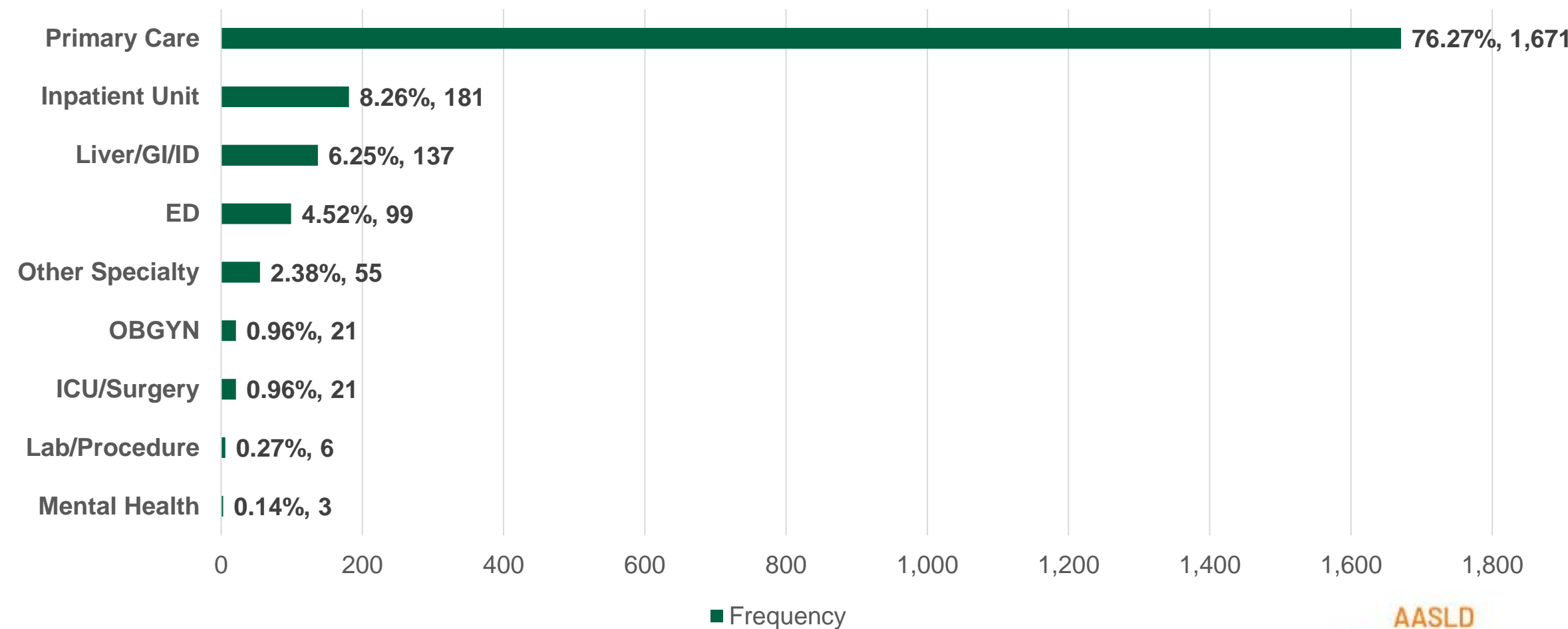


HBsAg to HDV Ab Reflex Testing Cascade, Unique Patients March – October 2024



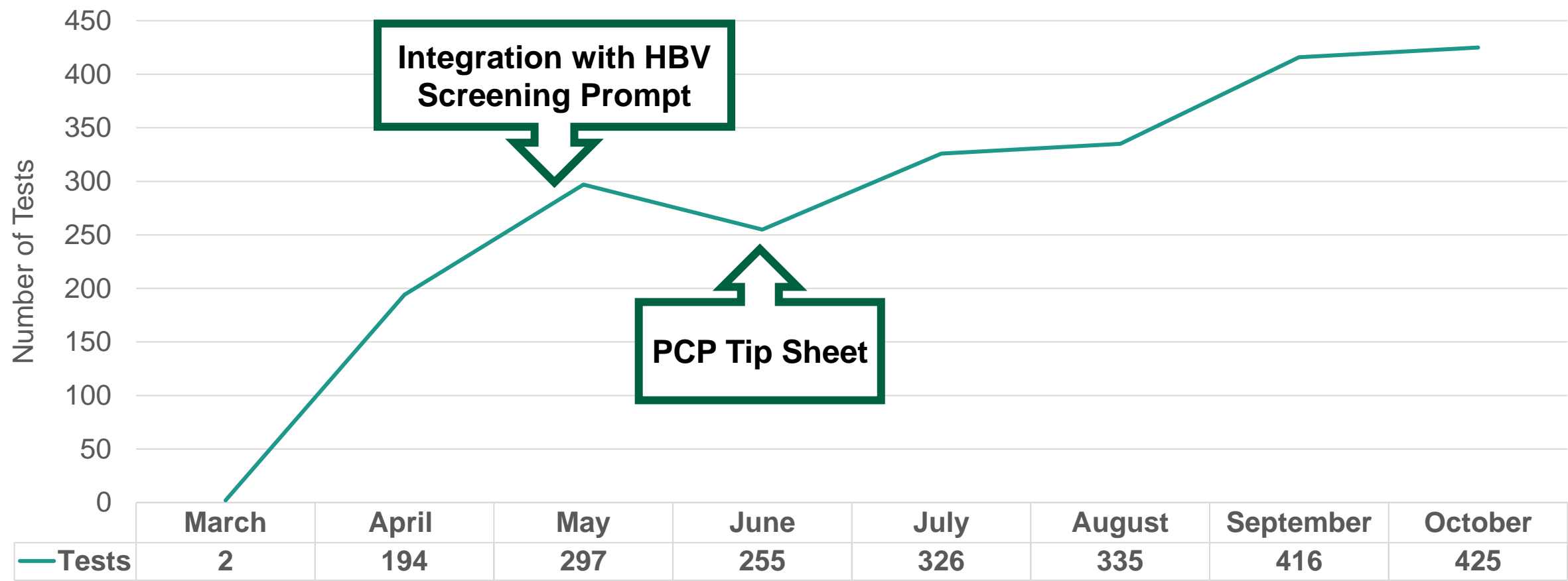
Reflex Testing by Department Type

Unique Patients Receiving HBsAg to HDV Ab Reflex Testing by Department Type
March – October 2024



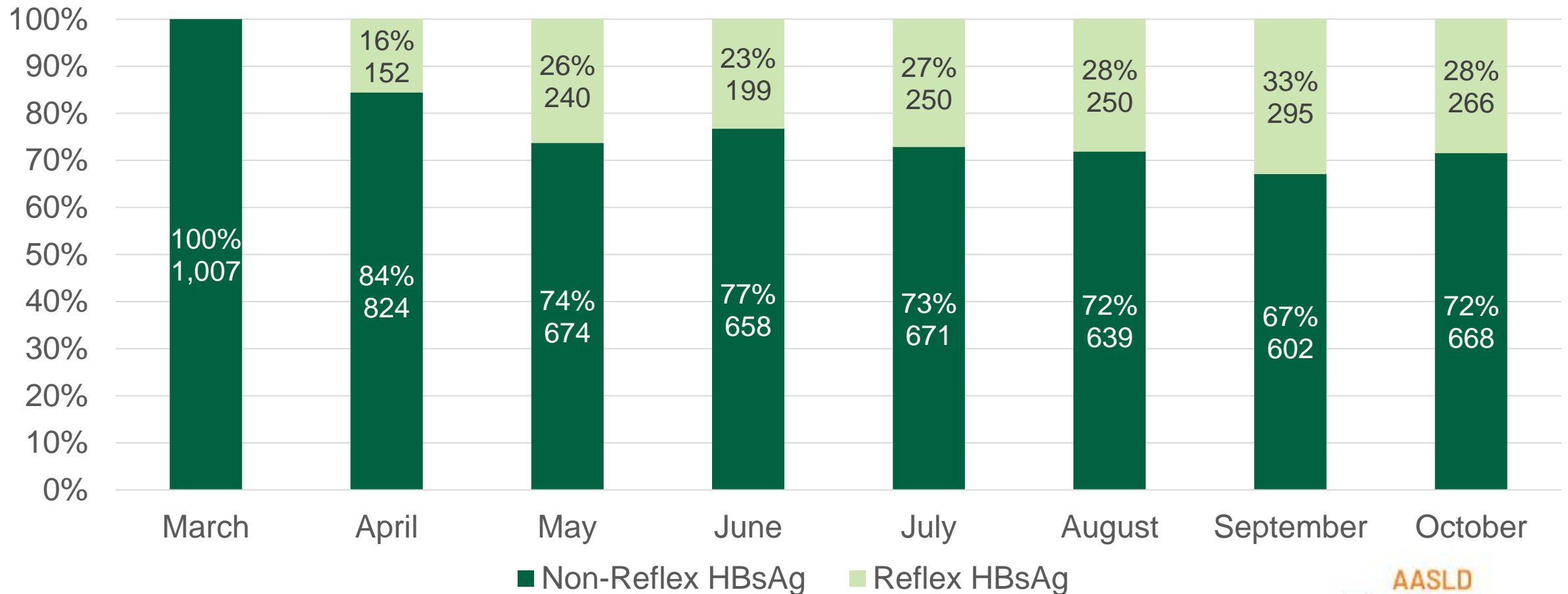
Reflex Uptake over Time

Number of HBsAg to HDV Ab Reflex Tests by Month
March – October 2024 (n = 2,250)



Reflex Uptake Over Time Compared to Non-Reflex HBsAg in Primary Care

Share of Reflex HBsAg Tests Ordered in Primary Care



Conclusions & Future Directions

Conclusions

- Reflex testing integrated into existing infrastructure **can increase screening rates and reduce provider burden.**
- **Improved efficiency** in follow-up testing time.
- **Potential savings:** can eliminate unnecessary HDV Ab tests ordered with first HBsAg test.

Future Directions

- Increase **provider education** to expand usage.
- Collaboration with **LabCorp for send-out clinics** (awaiting NYS/FDA approval of reflex assay).
- Further reflex from **HDV Ab+ to HDV PCR.**
- Identify diagnosed but lost-to-care HDV+ patients via **case-finding algorithm.***

*Ash N, et al., AASLD TLM 2024.

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EPIC Team:

Jimmy Wu, Kristie Heiden, Michael Fisher

Liver Team:

Lauren Alpert, Nina Rodriguez, Cecilia Katzenstein,
Dr. Andrea D. Branch, Dr. Douglas T. Dieterich,
Dr. Tatyana Kushner



HDV Community Advisory Board



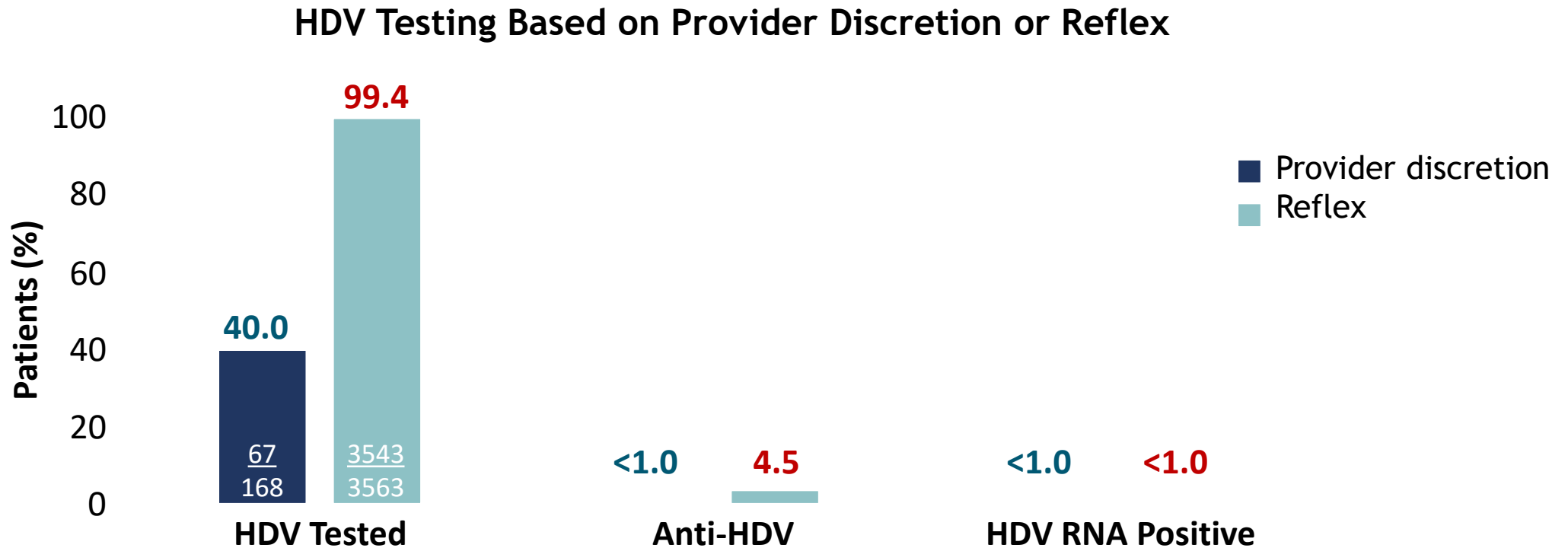
GILEAD





HBsAg-Positive Reflex to Anti-HDV

- Cross-sectional analysis of HDV testing among HBsAg-positive patients at 2 London Centers, 2005-2012



- Center with a reflex laboratory algorithm achieved anti-HDV testing of almost all first HBsAg-positive samples over a 12-yr period