



# Investigating Unresolved HIV Status during Endpoint Confirmation

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# Outline

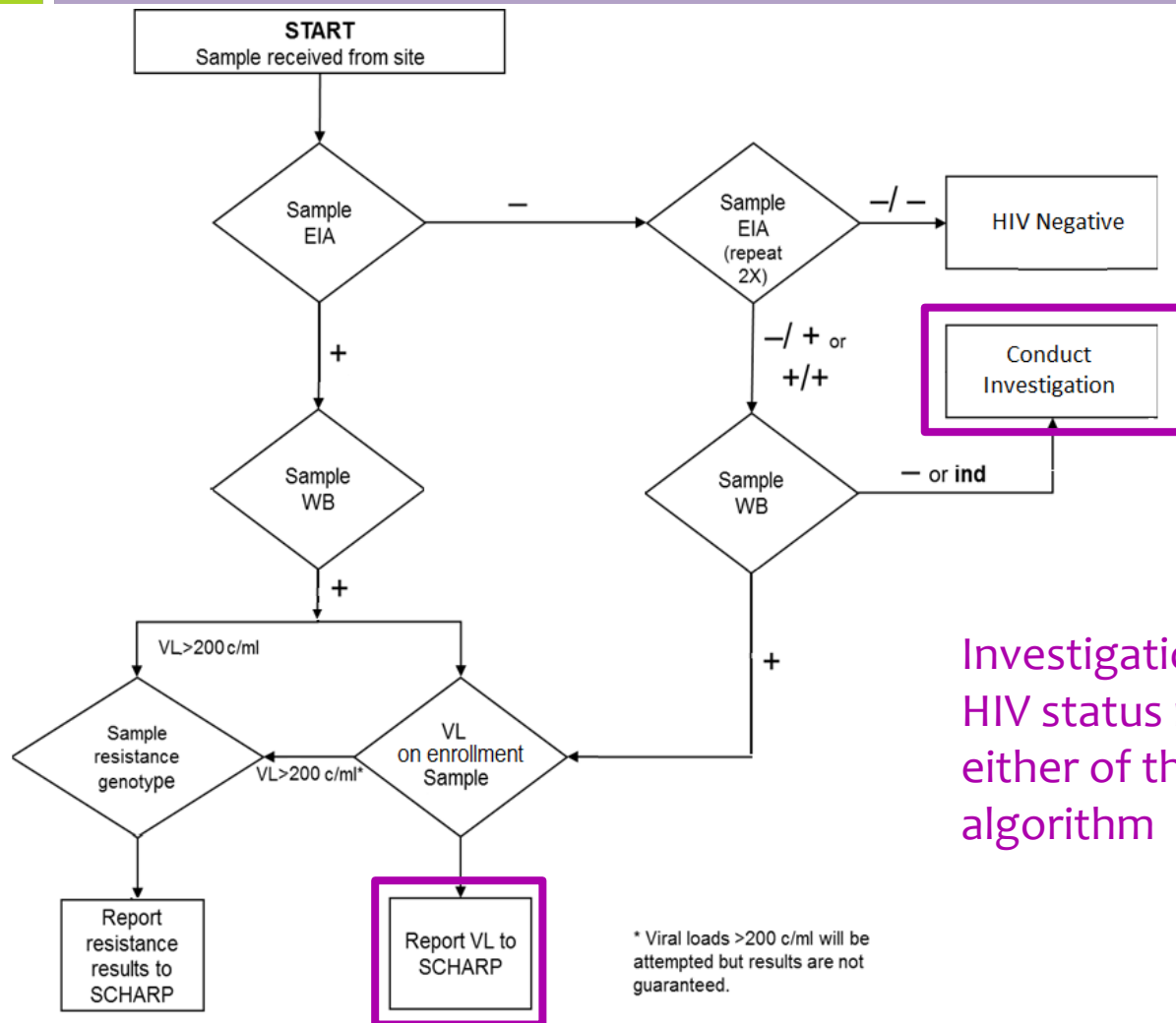
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1. Process of conducting investigations and resolving HIV status
2. Summary of investigations in VOICE
3. Case study examples and discussion
4. Lessons learned for ASPIRE

# VOICE Virology CORE Algorithm

- Virology CORE is responsible for confirming HIV status for all endpoints independently from sites
  1. Samples sent to Virology CORE
    - Seroconverter sample and enrollment sample for participant
    - Matched non-seroconverter sample
  2. Results are sent to SCHARP and compared to site results
  3. Discrepancies between results are investigated by NL and sent to the Endpoint Adjudication Committee for a decision

# VOICE/ASPIRE Virology CORE Algorithm



Investigations to resolve HIV status may occur at either of these points in the algorithm

\* Viral loads >200 c/ml will be attempted but results are not guaranteed.

# Investigation Reporting Process

- A summary of all available testing is compiled
  - Dates and visits tested are documented
  - Original results/images for all assays
  - Sites may be queried for additional information
- Data is submitted to the Endpoint Adjudication Committee (EAC) for a final outcome
- Corrective action may be initiated

# Sample Investigation Report

## MTN Endpoint Validation Investigation

**Reason for Investigation:** Positive EIA at enrollment; results do not match site results.

### Network Lab (Virology CORE) Testing History:

Visit	Specimen Date	Test*	Testing Date	Result
3.00	03/May/2011	EIA	03/13/12	POSITIVE
3.00	03/May/2011	WB	03/30/12	POSITIVE
3.00	03/May/2011	Rapid Test	03/30/12	POSITIVE
3.00	03/May/2011	VL	07/17/12	Not Detected (1:3 dilution)
6.00	26/Jul/2011	VL	07/17/12	Not Detected (1:3 dilution)
6.00	26/Jul/2011	Rapid Test	07/30/12	POSITIVE
6.00	26/Jul/2011	WB	07/10/12	POSITIVE
9.00	18/Oct/2011	WB	07/10/12	POSITIVE
9.00	18/Oct/2011	VL	05/25/12	Detected <40 copies/mL
9.00	18/Oct/2011	Rapid Test	07/30/12	POSITIVE
11.10	28/Jan/2012	WB	07/10/12	POSITIVE
11.10	28/Jan/2012	Rapid Test	07/30/12	POSITIVE

### Summary:

Specimen considered HIV negative until v11.0 at site. Specimen tested HIV positive by EIA and WB at Virology CORE at v3.0. Additional samples requested. All samples from later visit dates that were shipped to Virology CORE tested POSITIVE by WB. The v9.0 specimen tested positive for a VL = <40 copies/mL, detected. VL for v3.0 and v6.0 tested at a 1:3 dilution to conserve sample volume. HIV RNA levels were too low at all visits; therefore sequencing cannot be done to assess drug resistance or to compare virus populations at different visit dates.

# Major Types of Investigations

## HIV-infected at Enrollment by RNA PCR

- Participant is acutely infected prior to study start

## Enrollment Sample not Available

- RNA PCR on enrollment sample cannot be performed

## Discrepant Test Results

- Results at NL and at site are different
- Results from different tests at the same lab are different

# Investigations in VOICE

3

Enrollment sample not available

22

HIV- infected at enrollment

47

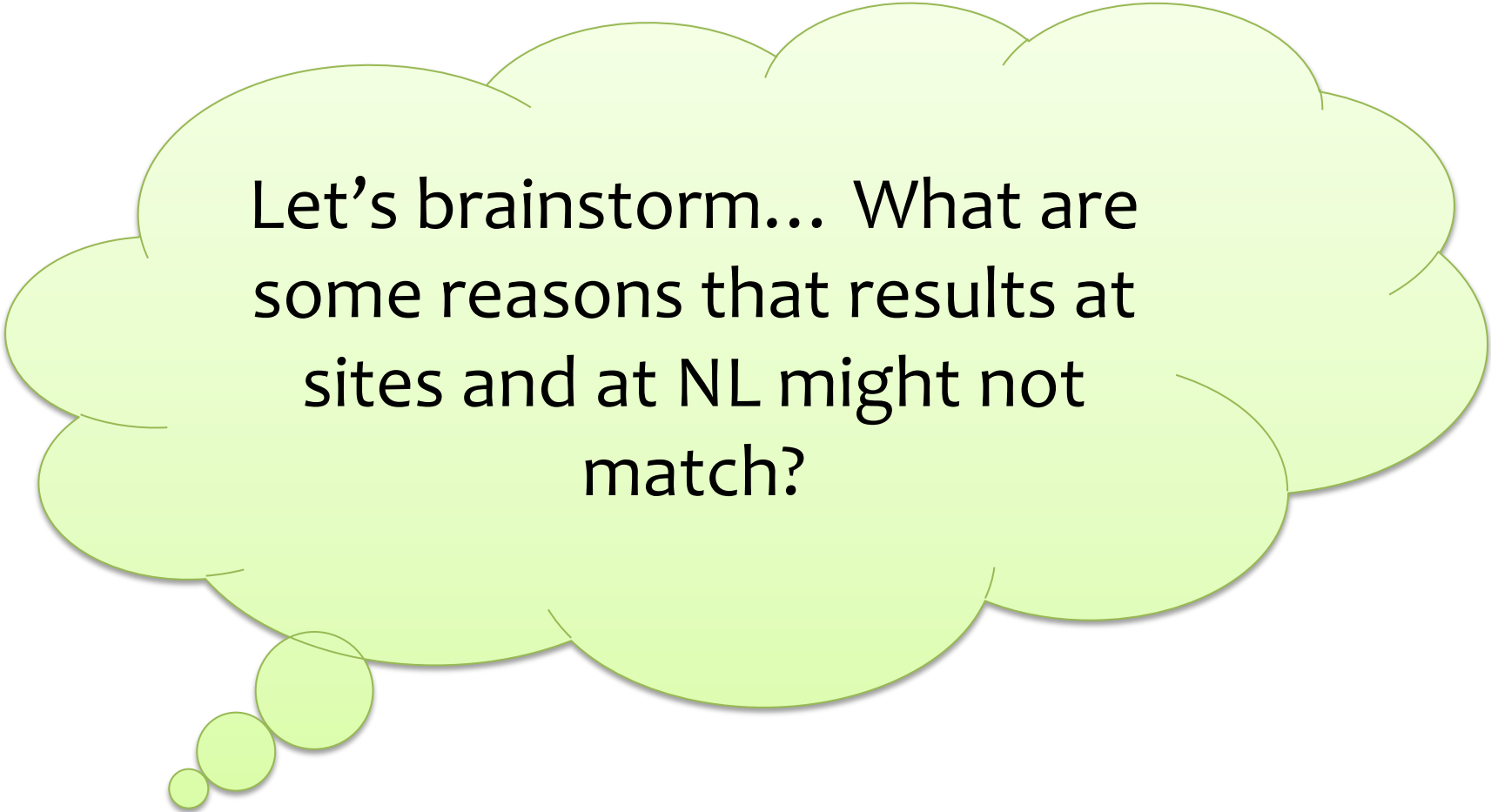
Discrepant test results

\* An additional 6 reports were prepared. Cases were solved without EAC intervention



# What causes discordant results?

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Let's brainstorm... What are some reasons that results at sites and at NL might not match?

# What causes discordant results?

Sites and NL use  
different assays  
for screening

Testing errors

Sample mix-ups

# Testing Errors

- The major testing error during VOICE occurred during screening
  - Rapid tests were not being performed properly
  - A non-FDA approved version of Unigold/Oraquick was used
  - Possible transcription errors

# How can we reduce testing errors?

- Ensure all SOPs are accurate and followed correctly
- Make sure all testing personnel are well-trained to perform assays and interpret results



Expertbriefings.com;



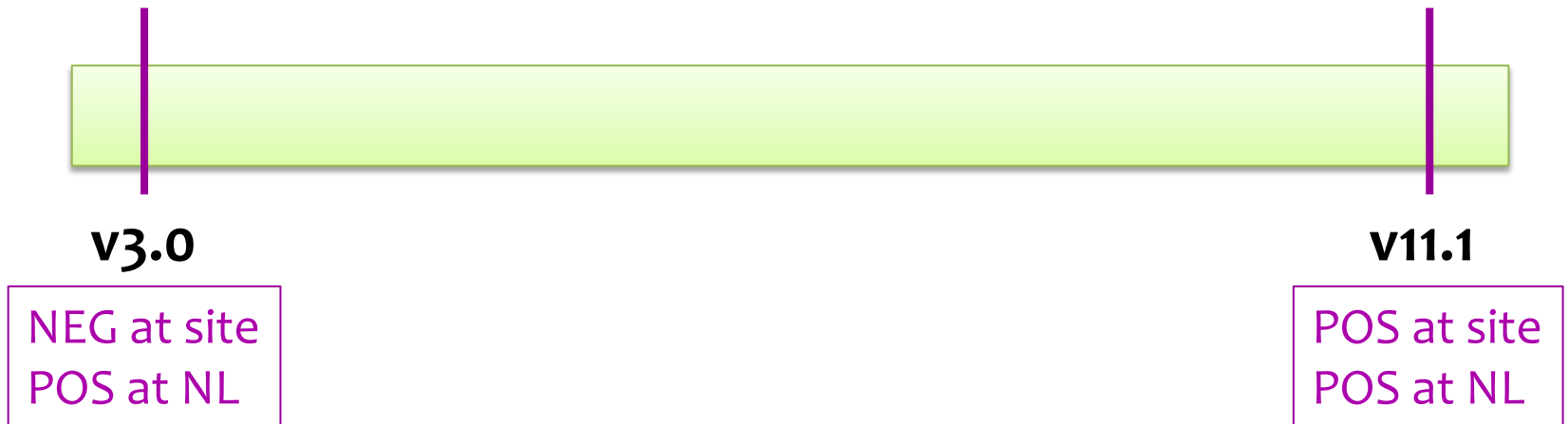
[usatoday30.usatoday.com/news/health/story/2012-07-03/fda-approves-hiv-home-tests/56002548/1](https://www.usatoday30.usatoday.com/news/health/story/2012-07-03/fda-approves-hiv-home-tests/56002548/1)

# Sample Mix-ups

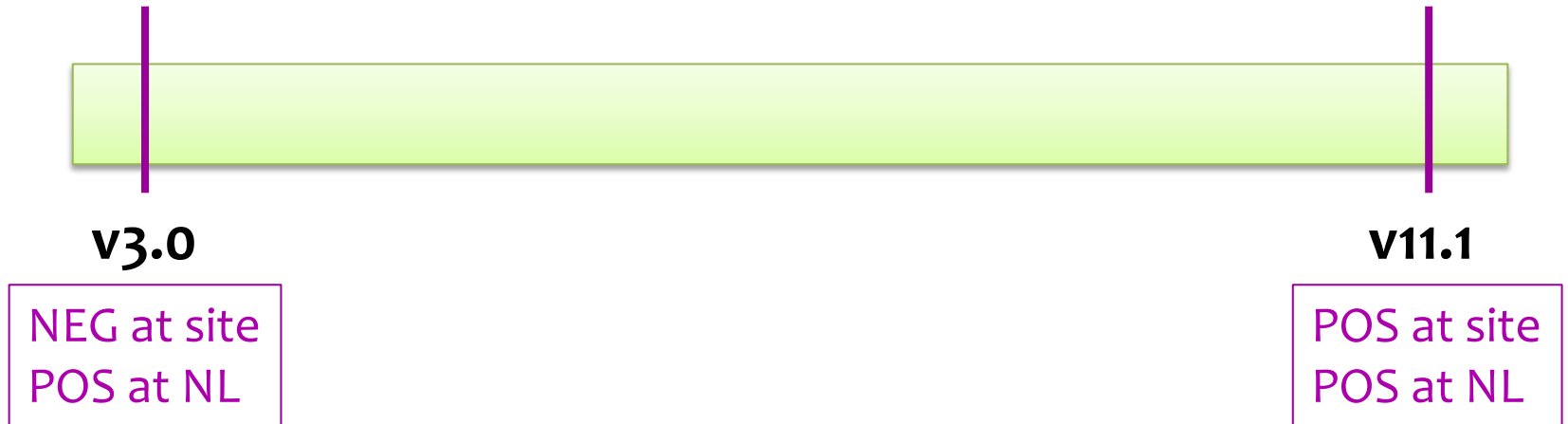
- Sample mix-ups occurred when...
  - Multiple tubes were labeled identically
  - Participant samples were labeled with information from a different participant
  - Multiple people coming in under the same name/PTID

# Case Study Example #1

A participant was identified POSITIVE at the site at v11.1. NL found the participant POSITIVE at v3.0 by viral load testing. What could explain how this participant was not identified as HIV-infected for 8 months even though HIV testing was done monthly?



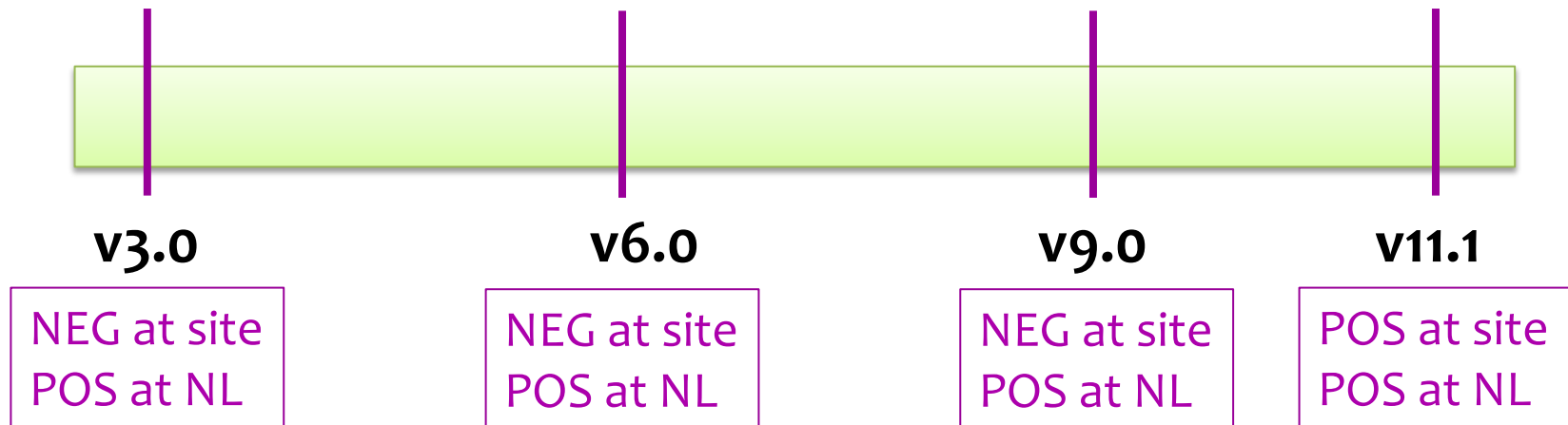
# Case Study Example #1



- Could it be a difference in the tests used between site and NL?
- Could it be a testing error?
- Could it be a sample mix-up?

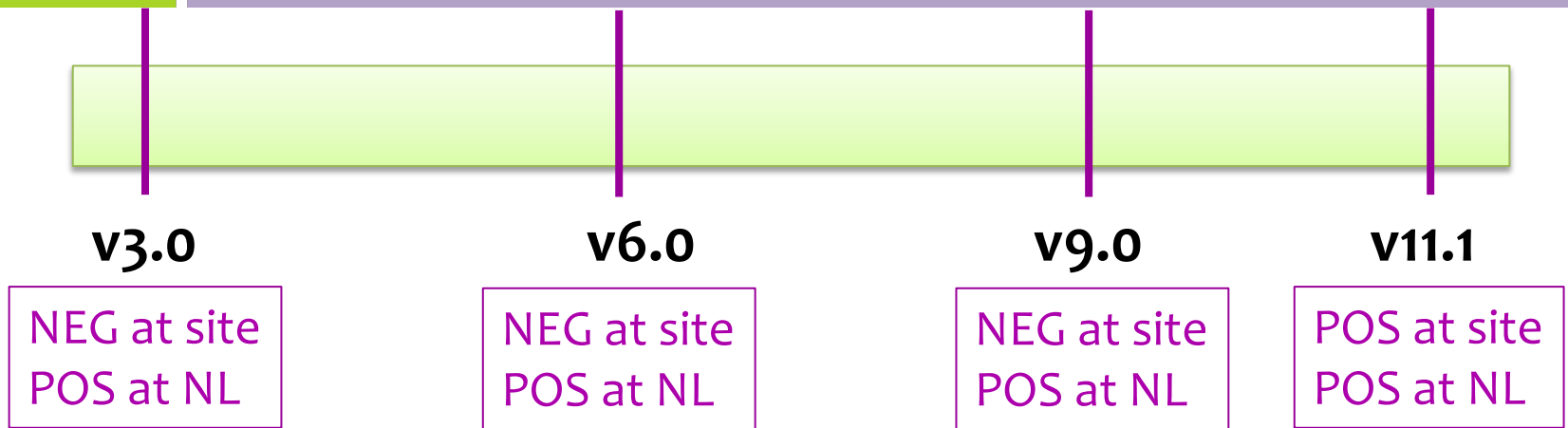
# Case Study Example #1

To investigate, NL requested samples in between v3.0 and v11.1 to test. They received 2 other visits, v6.0 and v9.0, both of which tested POSITIVE by EIA and WB at NL, but NEGATIVE by rapid test at the site.





# Case Study Example #1



- With this new information:
  - Could it be a difference in the tests used between site and NL?
  - Could it be a testing error?
  - ~~– Could it be a sample mix-up?~~

# Case Study Example #1

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How can we figure out if the site made a mistake and incorrectly called this participant NEGATIVE, or if there was no error and the NL's tests are able to detect that this participant is POSITIVE?

# Case Study Example #1

NL performed rapid tests using the same brand the site did, and found the participant to be POSITIVE at all four visits.

- With this new information:
  - ~~Could it be a difference in the tests used between site and NL?~~
  - Could it be a testing error?

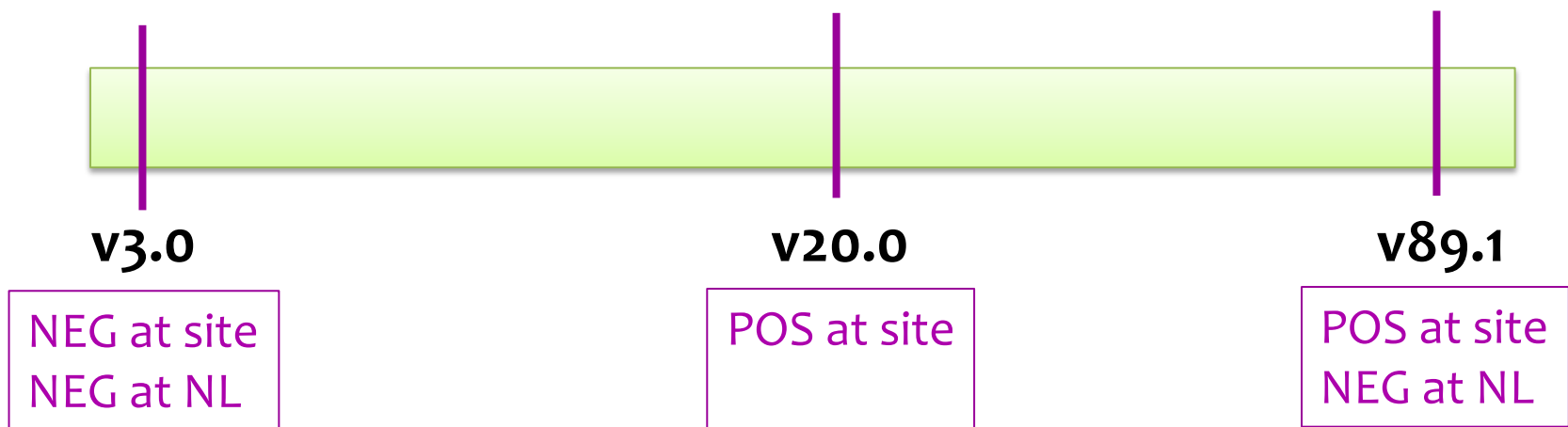
# Case Study Example #1

In this example, the site was interpreting rapid test results incorrectly.

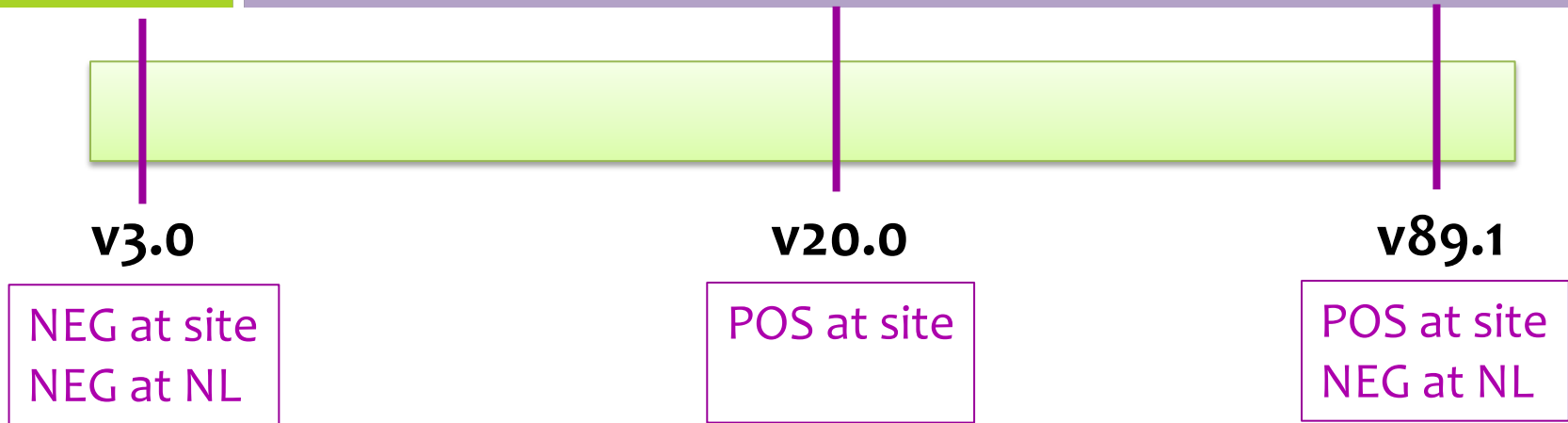
- Faint bands on rapid tests were called negative
- SOPs were modified and personnel were retrained
- NL performed 100% QC to ensure that no other errors had happened

# Case Study Example #2

- A participant was identified POSITIVE at the site at v89.1. NL found the participant to be NEGATIVE at v89.1 by 3xEIA, WB, and VL. The site was queried and v20.0 also tested POSITIVE at the site.



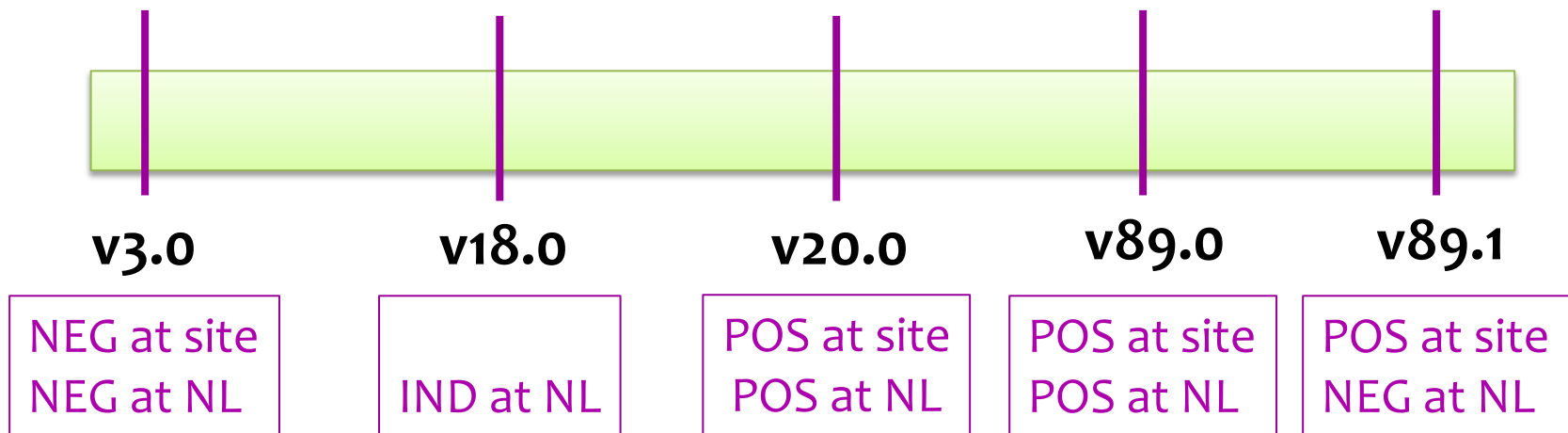
# Case Study Example #2



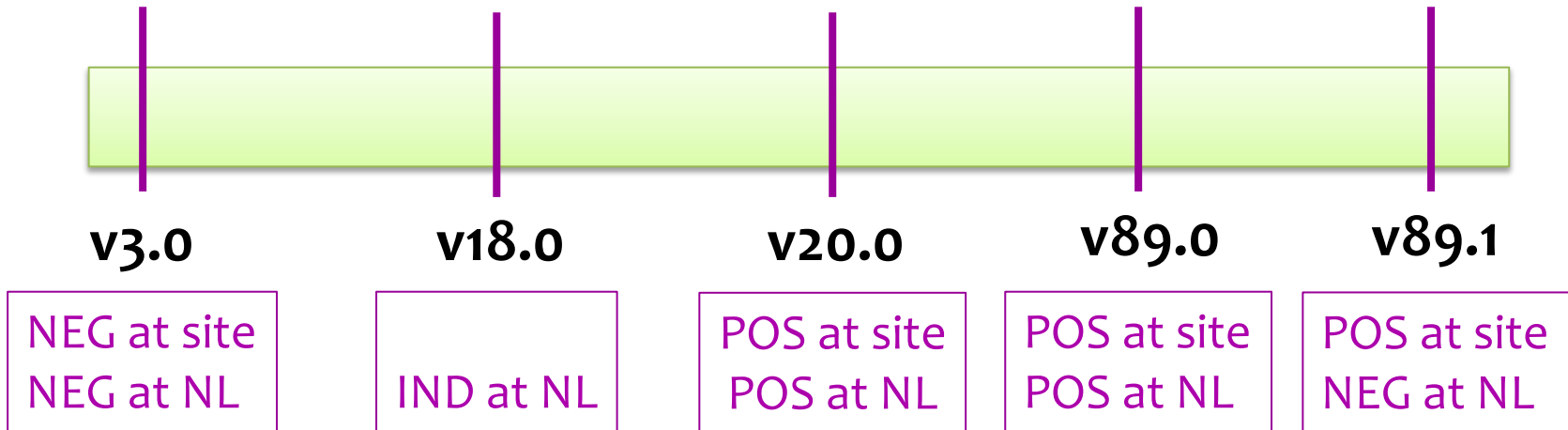
- ~~– Could it be a difference in the tests used between site and NL?~~
- Could it be a testing error?
- Could it be a sample mix-up?

# Case Study Example #2

- To investigate, NL requested samples in between v3.0 and v89.1 to test. They received 3 other visits, v18.0, v20.0, and v89.0.



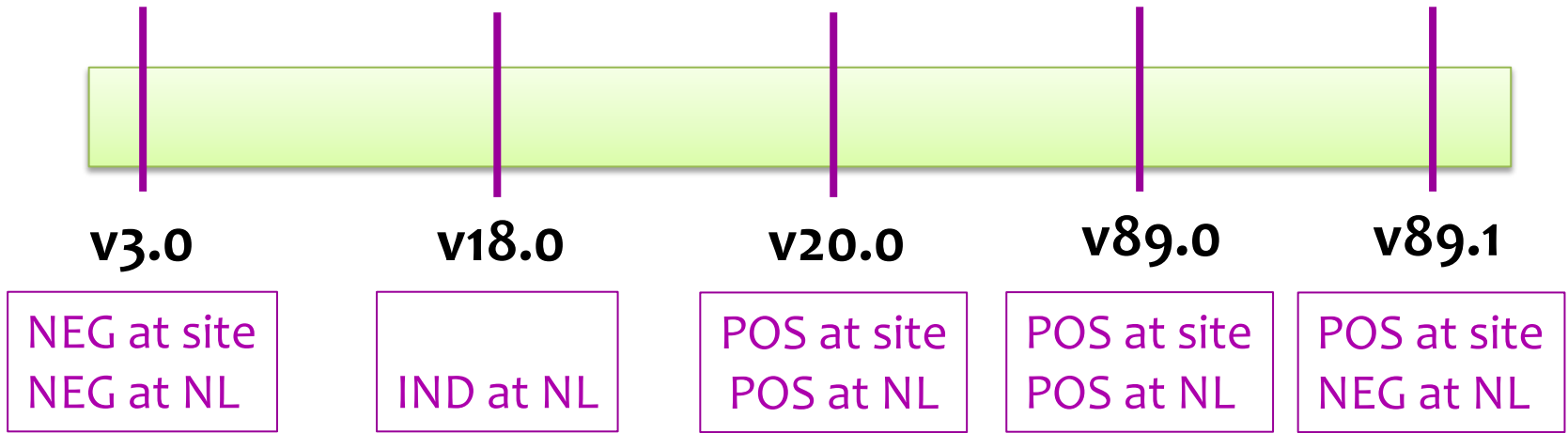
# Case Study Example #2



- With this new information:
  - ~~Could it be a testing error?~~
  - Could it be a sample mix-up?



# Case Study Example #2



Is this participant truly POSITIVE  
or truly NEGATIVE at v89.1?

# Case Study Example #2

- EAC found this participant to be HIV-infected and concluded that a sample mix-up occurred at v89.1.
- Questions remain...
  - Who does the sample at NL belong to?
  - Where are this participant's real v89.1 samples?
  - Was another participant told they were HIV-positive because of the mix-up?

# Lessons from VOICE to ASPIRE

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- When we perform our tests properly, we:
  - ✓ correctly diagnose participants
  - ✓ get proper care sooner for patients who become infected
  - ✓ have stronger data for how well the study is working
  - ✓ have fewer investigations

# ASPIRE so far..

Everyone is doing a great job!



# Acknowledgements

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