INSTI Resistance in the Setting of CAB-LA PrEP

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June 16, 2024

2024 HPTN Annual Meeting

Presentation Highlights

HPTN
HIV Prevention Trials Network

1. What is the main issue the presentation addresses?

- Long-acting cabotegravir (CAB-LA) is highly effective for HIV prevention
- This presentation will provide an overview of HIV drug resistance in persons who acquire HIV infection in the setting of CAB-LA PrEP

Presentation Highlights

2. What are the key findings?

- It can be difficult to detect and confirm HIV infections with CAB-LA PrEP. This makes it more likely that drug resistance will emerge before HIV infection is confirmed and treatment is started.
- In HPTN 083, most participants who developed resistance to CAB-LA had cross-resistance to other drugs that could impact their response to INSTI-based ART.

Presentation Highlights

3. How does the research advance HIV prevention efforts?

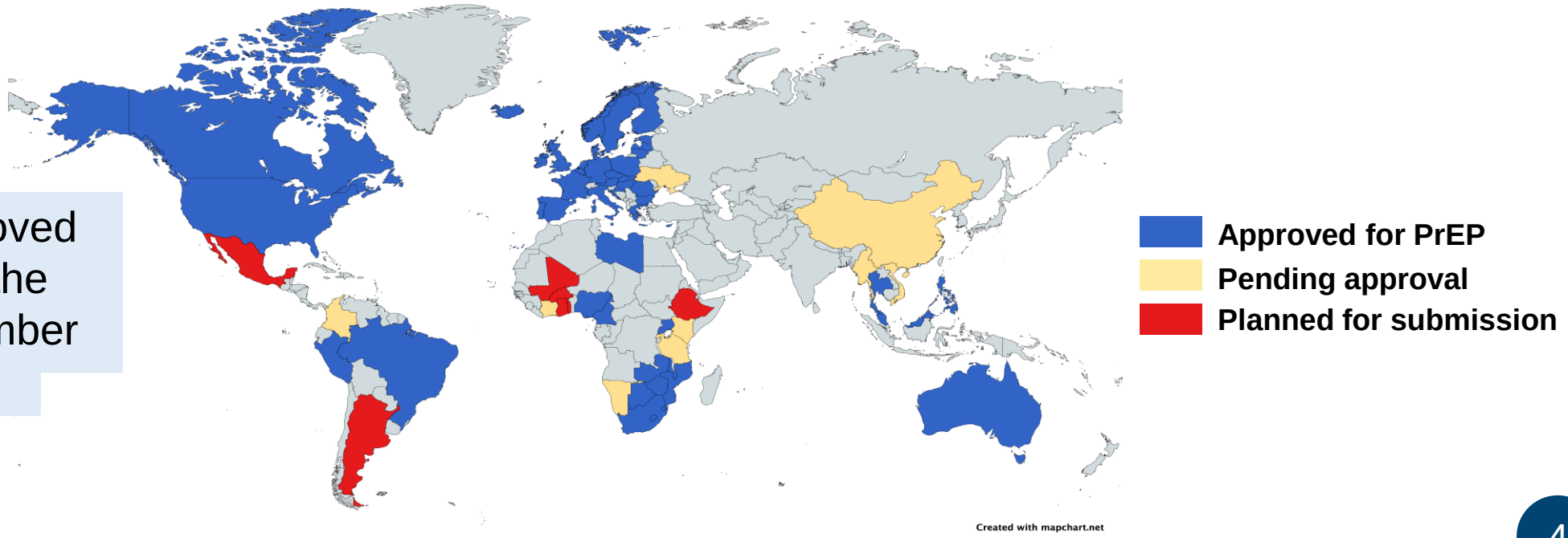
- Understanding HIV drug resistance in the setting of CAB-LA PrEP can help guide recommendations for treating CAB-LA breakthrough infections.

HPTN 083 and HPTN 084

HPTN 083 and HPTN 084 demonstrated that CAB-LA was superior to daily oral TDF/FTC for HIV prevention

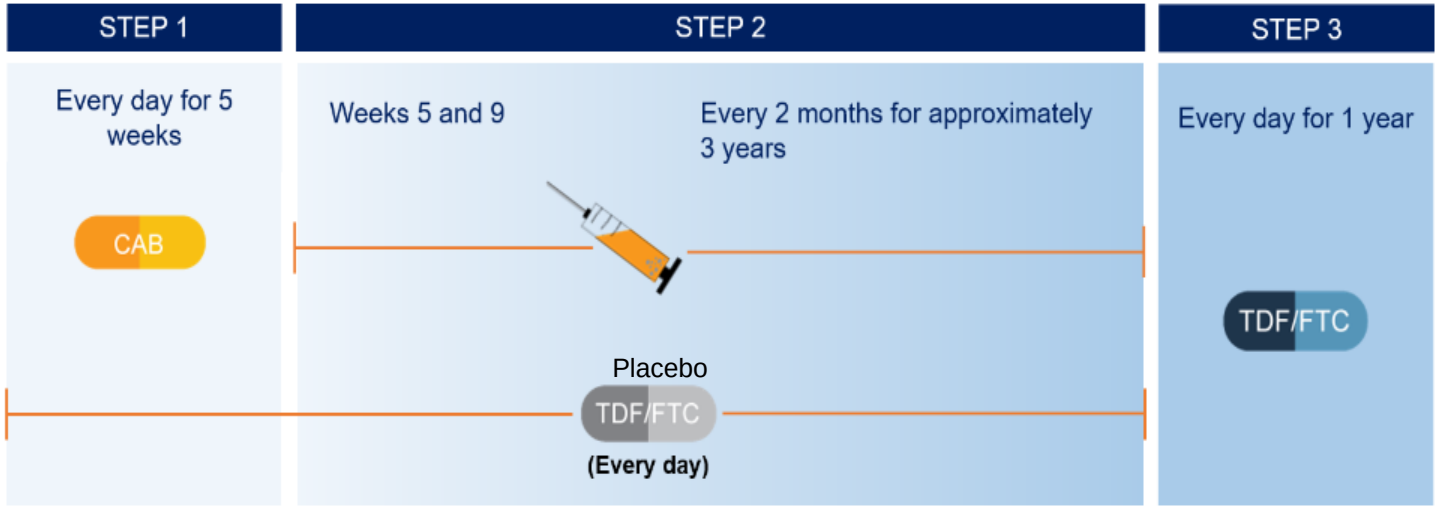
HPTN 083: MSM and TGW in the U.S., Latin America, Africa and Asia
HPTN 084: cisgender women in Africa

CAB-LA was approved for HIV PrEP by the U.S. FDA in December 2021



AVAC Country Planning for Product Introduction Matrix:
https://app.powerbi.com/view?r=eyJrIjoiMzc4ZWQwZGMtZTk4Yi00MTY4LWJiNGItNjRkNGRhNTZiMzIzIiwidCI6ImFmNjQ0ZDZjLWFlYmUtNDRkMi1hNDc2LTczOTdlZmJhMWEzZiIsImMiOjN9

HPTN 083 and HPTN 084 – CAB Arm



Participants continued the randomized study regimen while awaiting the open label extension study (OLE)

OLE

- Participants chose TDF/FTC or CAB-LA
- HIV VL testing at every visit

HIV testing at study sites

RNA testing within 14 days before enrollment

Rapid and Ag/Ab tests at enrollment and follow-up visits

HIV Infections in HPTN 083 and HPTN 084

Blinded phase plus 1st unblinded year

Type of case	HPTN 083	HPTN 084
Person-years follow-up, CAB arm	4660	3334
Infected despite on-time injections	**6**	**0**
Other infections • Baseline infections • Oral phase infections • Infected after ≥1 delayed injection • No CAB exposure within 6 months	28	7
Total	**34**	**7**

Marzinke, JID 2021; 224:1581
Eshleman, JID 2022; 225:1749
Eshleman, JID 2022; 226:2170
Marzinke, AAC 2023; 7(4):e0005323
Delany-Moretlwe, AIDS 2022; Abstract OALBX0107

Long-acting Early Viral Inhibition (LEVI)

- HIV rapid tests and Ag/Ab tests often failed to detect HIV infection in the setting of CAB-LA PrEP
- Viral suppression and delayed/diminished Ab expression can persist for months after infection, even after injections are discontinued

Delayed detection of HIV infection
→ Unnecessary CAB-LA injections
→ Delayed ART initiation
→ Potential to impact personal health or on-going HIV transmission
→ **Emergence of INSTI resistance**

We coined the term “long-acting early viral inhibition” (LEVI) to describe the biology and laboratory features of early HIV infection in the setting of long-acting PrEP agents

Eshleman, CROI 2022, Abstract LB095

Evaluation of HIV Drug Resistance

HIV drug resistance testing was performed retrospectively for HIV infections that occurred during the blinded phase and first unblinded year of HPTN 083

- VL >500 c/mL - GenoSure PRIme assay (Monogram Biosciences)
- VL <500 c/mL - Low VL INSTI SGS assay (Lou Halvas, Univ of Pittsburgh)
- Interpretation of genotyping results - Stanford HIV Drug Resistance Database

Marzinke, JID 2021; 224:1581
Eshleman, JID 2022; 226:2170
Marzinke, AAC 2023; 7(4):e0005323

INSTI Resistance with CAB-LA PrEP

In HPTN 083, major INSTI RAMs were detected in 10 (63%) of the 16 cases where the 1st HIV positive visit was within 6 months of CAB-LA injection

This included all 6 cases with on-time injections

Major INSTI RAMs were not observed when the 1st HIV positive visit was >6 months after CAB administration (this timeline may be longer in ciswomen)

Landovitz, Lancet HIV. 2023;10(12):e767-e778
Marzinke, AAC 2023; 7(4):e0005323

Timing of INSTI Resistance

INSTI resistance mutations often emerge early when the viral load is low

Median days after the 1st HIV positive visit: 38 days (IQR: 21-56)

Median viral load: 148 c/mL (IQR: 77-1,011)

Retrospective testing with a sensitive RNA assay detected most infections before INSTI resistance emerged

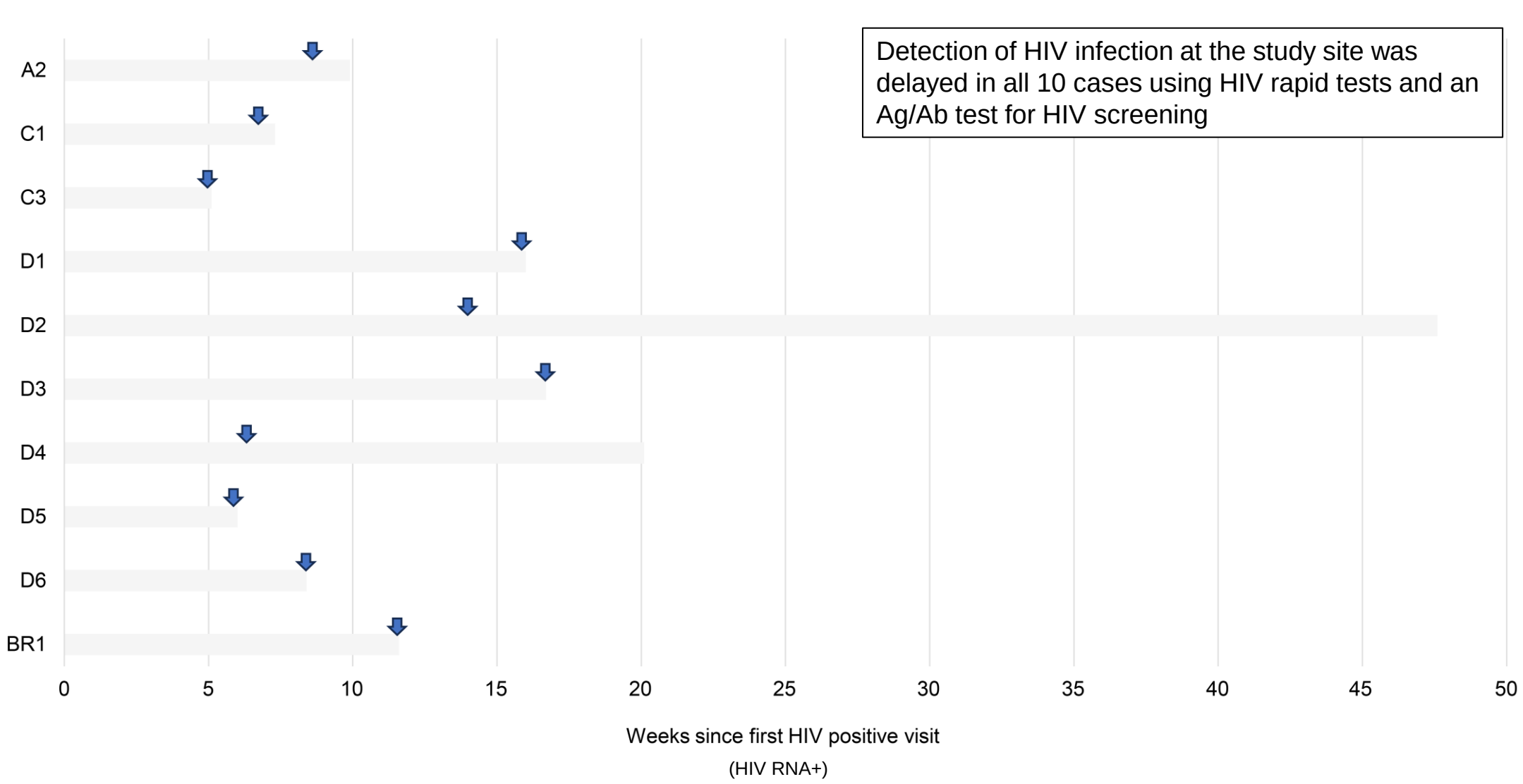
”Missed HIV infection” provides an opportunity for selection and accumulation of major INSTI RAMs

HPTN 083: Major INSTI RAMs Detected

Case ID	HIV subtype	Major INSTI RAMs (1st HIV positive visit → site detection)
A2	C	None → **E138K, Q148K**
C1	B	None → **Q148R** → **E138K**, **G140S**, **Q148R**
C3	B	None → **E138A, Q148R**
D1	B	**N155H** → **Q148R, N155H** → **N155H**, **R263K**
D2	B	→ **N155H**
D3	B/F	None → **R263K**
D4	C	→ **Q148R** → **E138K, Q148R** → **G140A, Q148R**
D5	F	**R263K**
D6	AE	None → **Q148R**
BR1	BC	None → **Q148R**

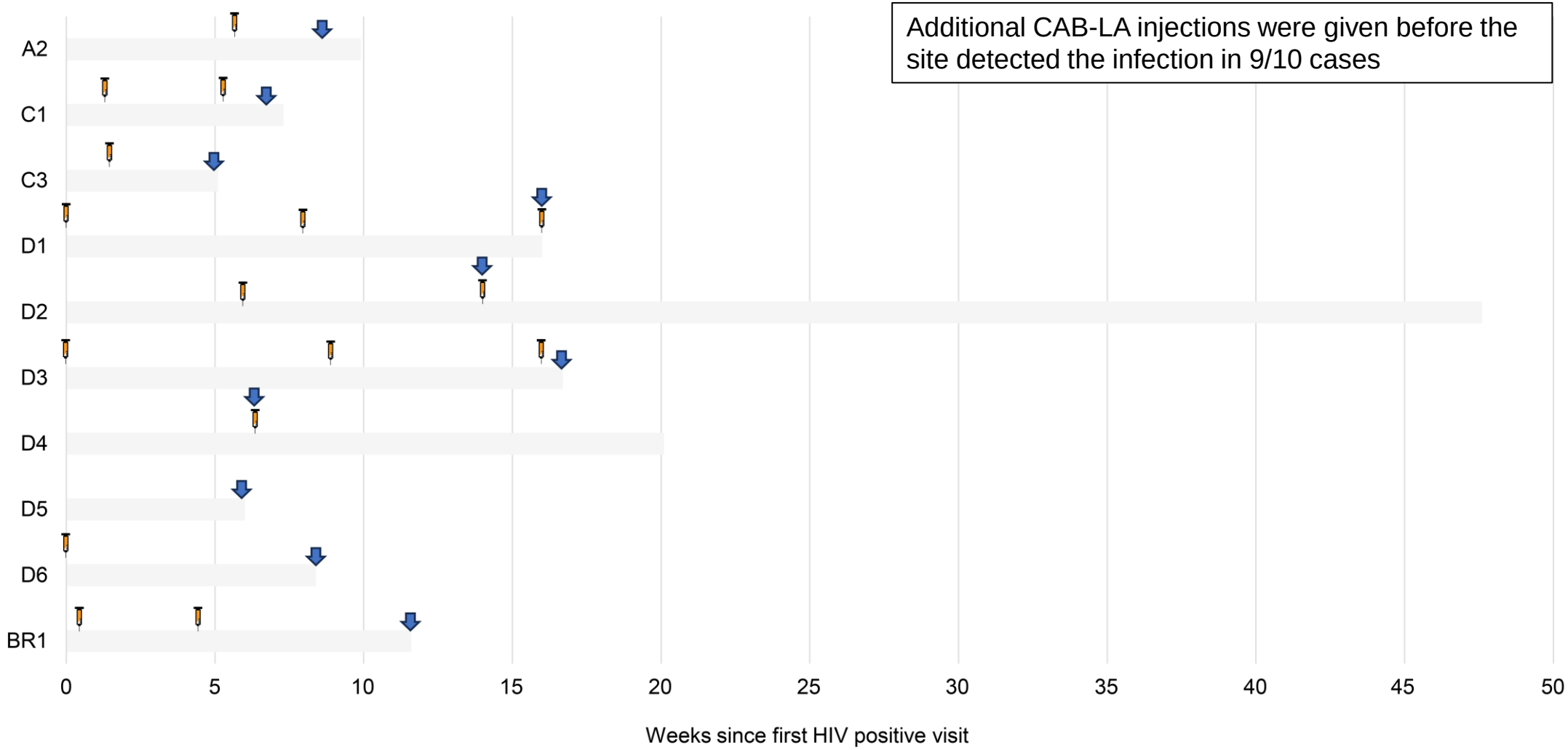
5 started DRV-based ART
4 started EFV-based ART
1 started DTG-based ART (C1)

Delayed Detection of Infection



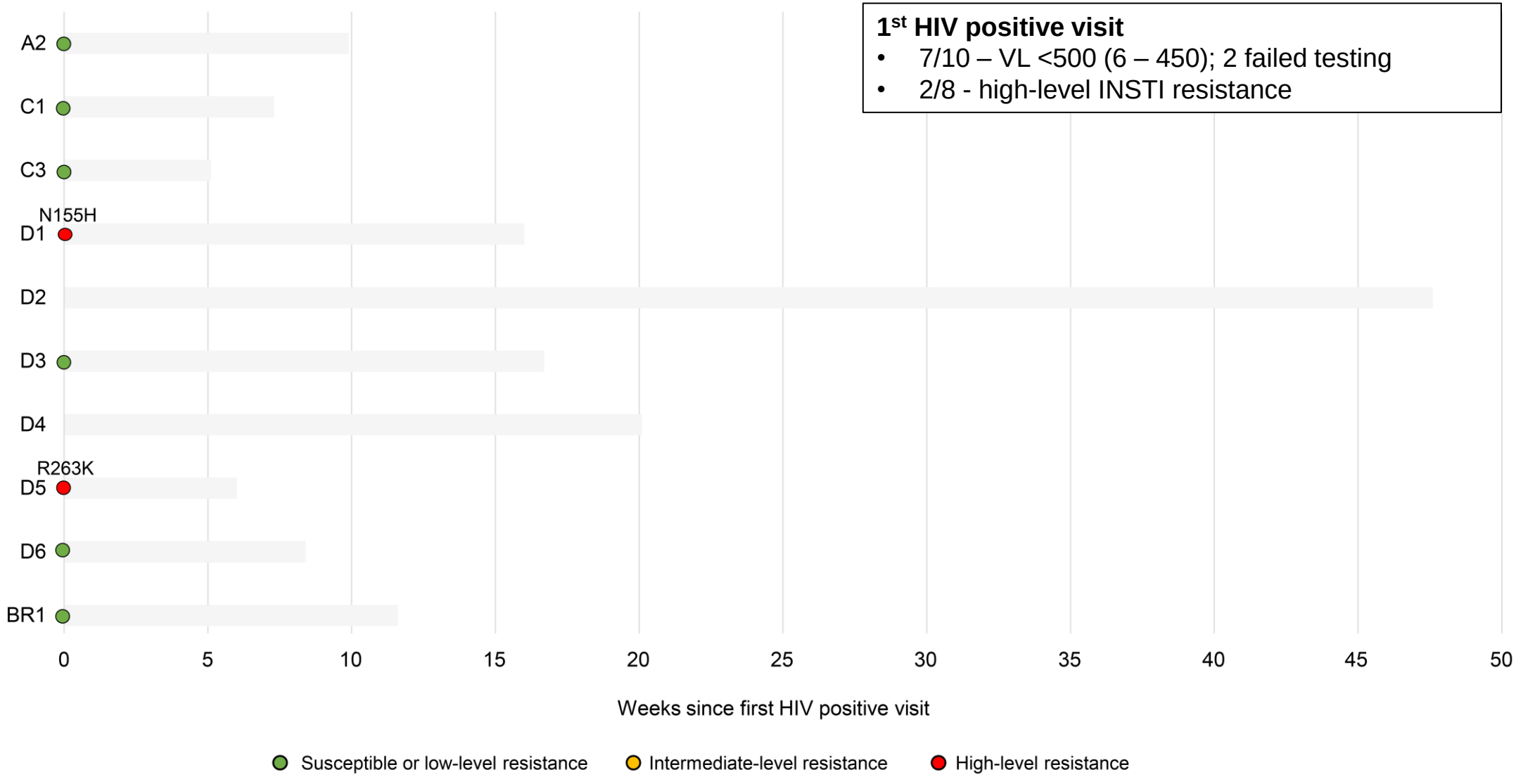
Detection of HIV infection at the study site was delayed in all 10 cases using HIV rapid tests and an Ag/Ab test for HIV screening

Injections Given After HIV Infection

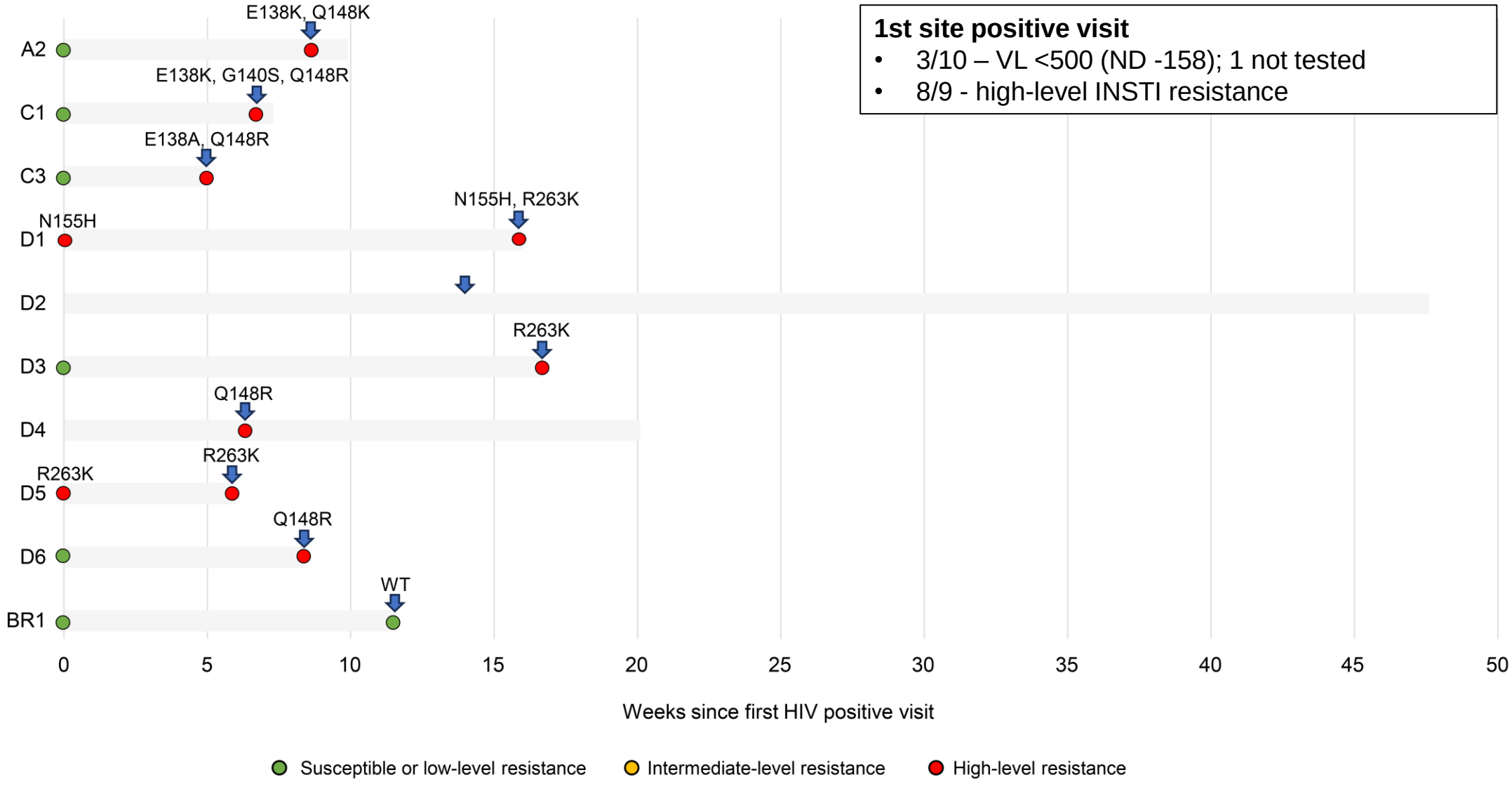


Additional CAB-LA injections were given before the site detected the infection in 9/10 cases

Predicted INSTI Resistance, First HIV POS Visit



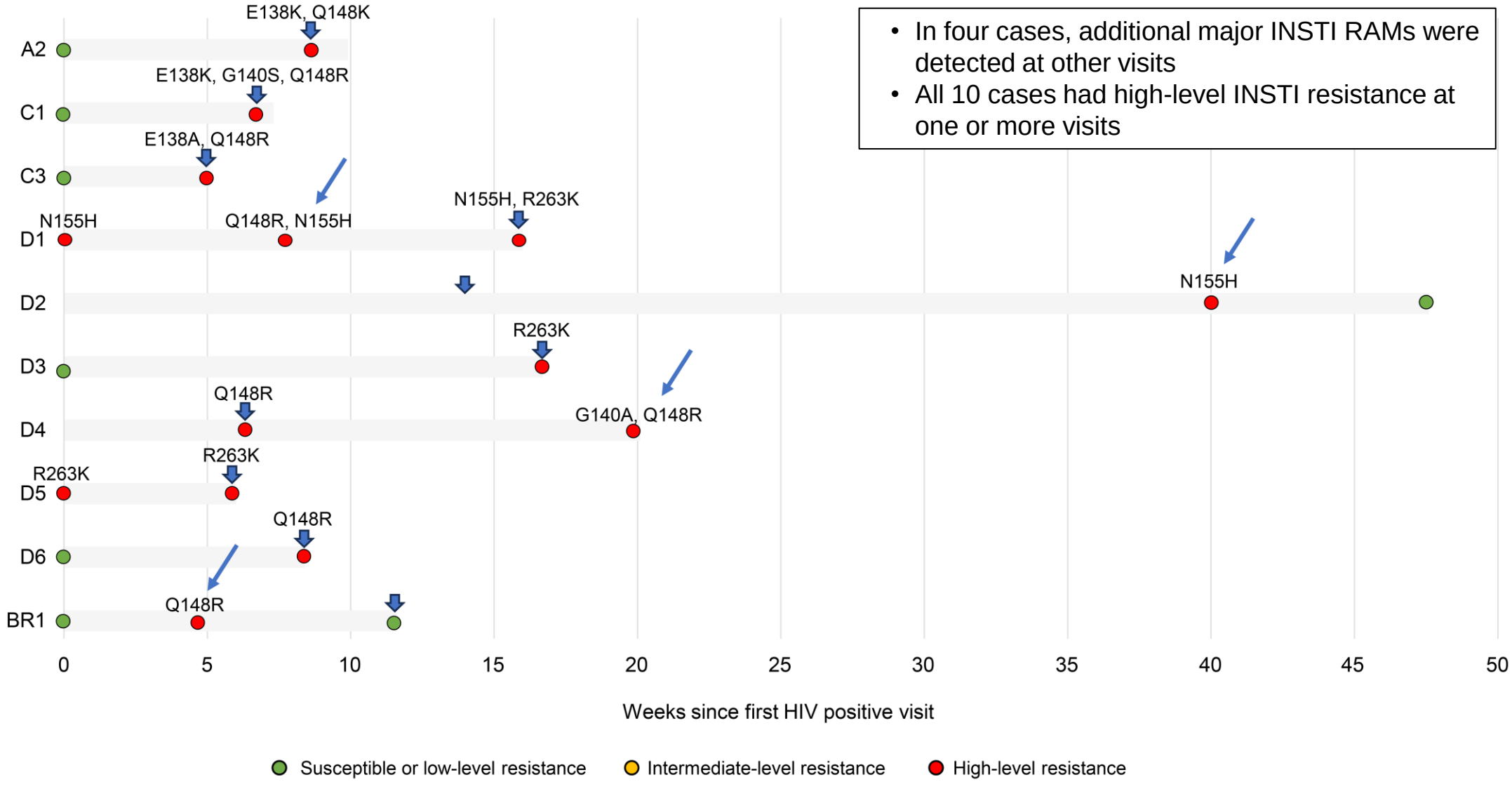
Predicted INSTI Resistance, First Site POS Visit



1st site positive visit

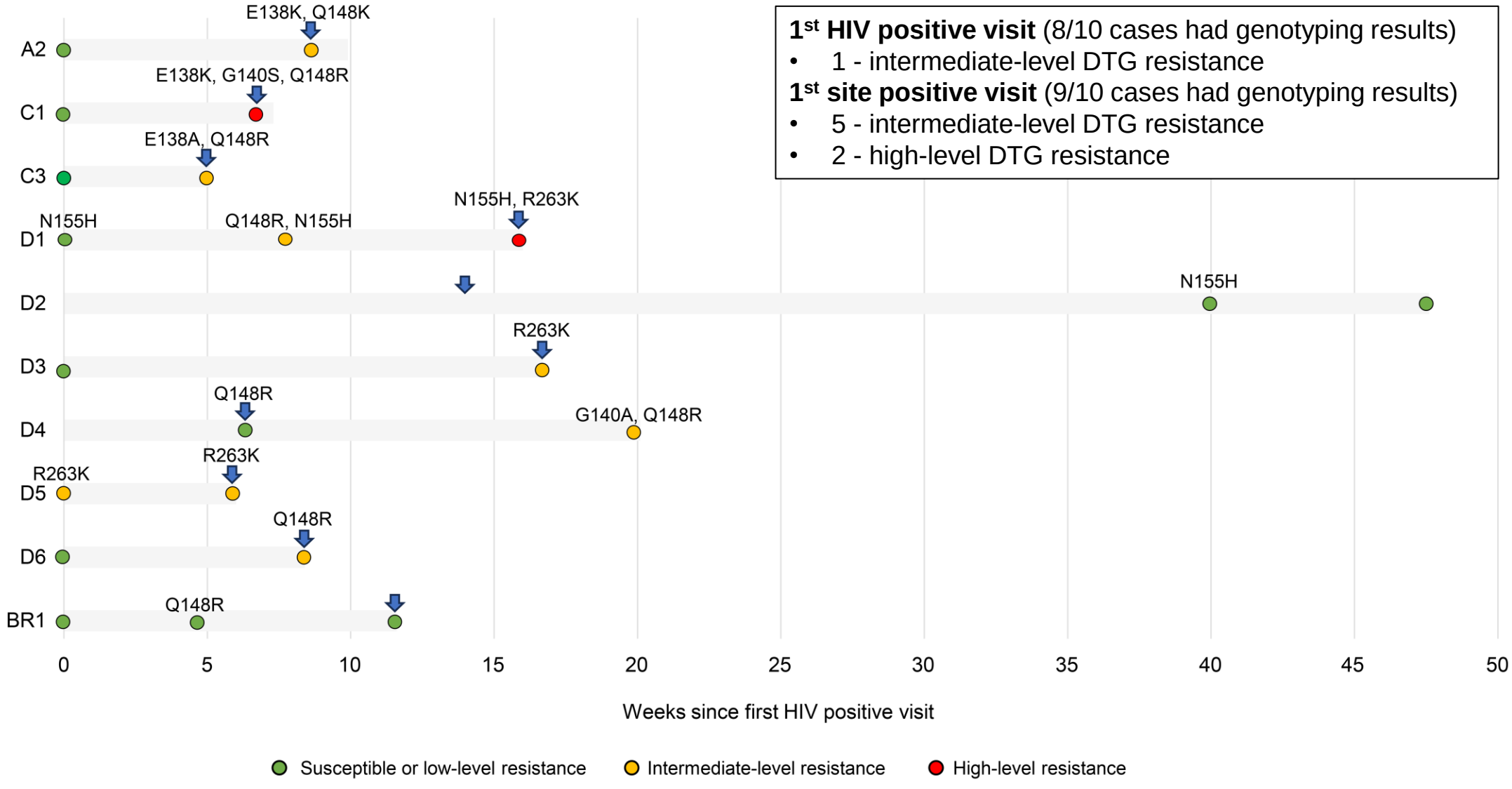
- 3/10 – VL <500 (ND -158); 1 not tested
- 8/9 - high-level INSTI resistance

Predicted INSTI Resistance, Other Visits



- In four cases, additional major INSTI RAMs were detected at other visits
- All 10 cases had high-level INSTI resistance at one or more visits

Predicted DTG Resistance



1st HIV positive visit (8/10 cases had genotyping results)
- 1 - intermediate-level DTG resistance

1st site positive visit (9/10 cases had genotyping results)
- 5 - intermediate-level DTG resistance
- 2 - high-level DTG resistance

Key Findings

083: blinded phase and 1st unblinded year

Major INSTI RAMs were detected in:

- 10 (38%) of the 26 cases
- 10 (63%) of the 16 cases with the 1st HIV positive visit within 6 months of CAB injection
- All cases with on-time injections

Intermediate or high DTG resistance was predicted in 8 of the 10 cases with major INSTI RAMs

Resistance usually emerges when HIV viral load is too low to assess with standard HIV genotyping assays

Key Points

1. HIV infection is rare in those receiving on-time CAB injections.

2. Delayed detection of infection using standard HIV screening assays allows for accumulation of INSTI RAMs with increasing resistance.

3. Further research is needed to assess the response to INSTI-based ART in persons who acquire HIV infection in the setting of CAB-LA PrEP.

Acknowledgments

Collaborators/investigators/co-authors
Participating laboratories
Study team and participants

Overall support for the HPTN is provided by NIAID, Office of the Director, NIH (NIAID, NIDA, NIMH, NICHD) UM1AI068619, UM1AI068617, UM1AI068613

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