Performance Evaluation of Determine™ HIV-1/2 Ag/Ab Combo in plasma and whole blood from early HIV-1 infections

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FDA-approved Ag/Ab HIV-1/2 screening assays

Assay	Manufacturer	specimen type	p24 detection	System
ADVIA Centaur HIV Ag/Ab Combo	**SIEMENS**	serum	with Ab	ADVIA Centaur or Centaur XP
ARCHITECT HIV Ag/Ab Combo	**Abbott**	serum/plasma	with Ab	ARCHITECT
GS HIV Combo Ag/Ab EIA	**Bio-Rad**	serum/plasma	with Ab	Evolis/automated microplate or manual
Bio-Plex 2200 HIV Ag-Ab	**Bio-Rad**	serum/plasma	differentiation	BioPlex 2200

- Instrumented or plate-based formats
- from ~30 min to 3 hours
- Not approved for blood or plasma donor screening

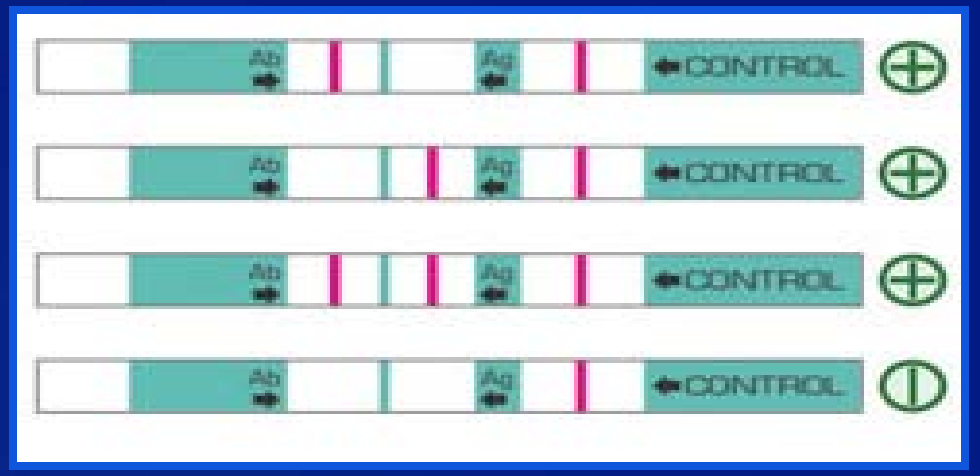
Alere Determine HIV-1/2 Ag/Ab Combo (DC)

- Manufacturer: Alere Scarborough, Inc.
- *In vitro*, visually read, rapid qualitative immunoassay
- Detection of HIV-1 p24 antigen and HIV-1/HIV-2 antibodies
- Point-of-care test to aid in the diagnosis of infection with HIV-1 and HIV-2, including an acute HIV-1 infection
- It may distinguish acute HIV-1 infection from established HIV-1 infection when the specimen is positive for HIV-1 p24 antigen and negative for anti-HIV-1 and anti-HIV-2 antibodies*

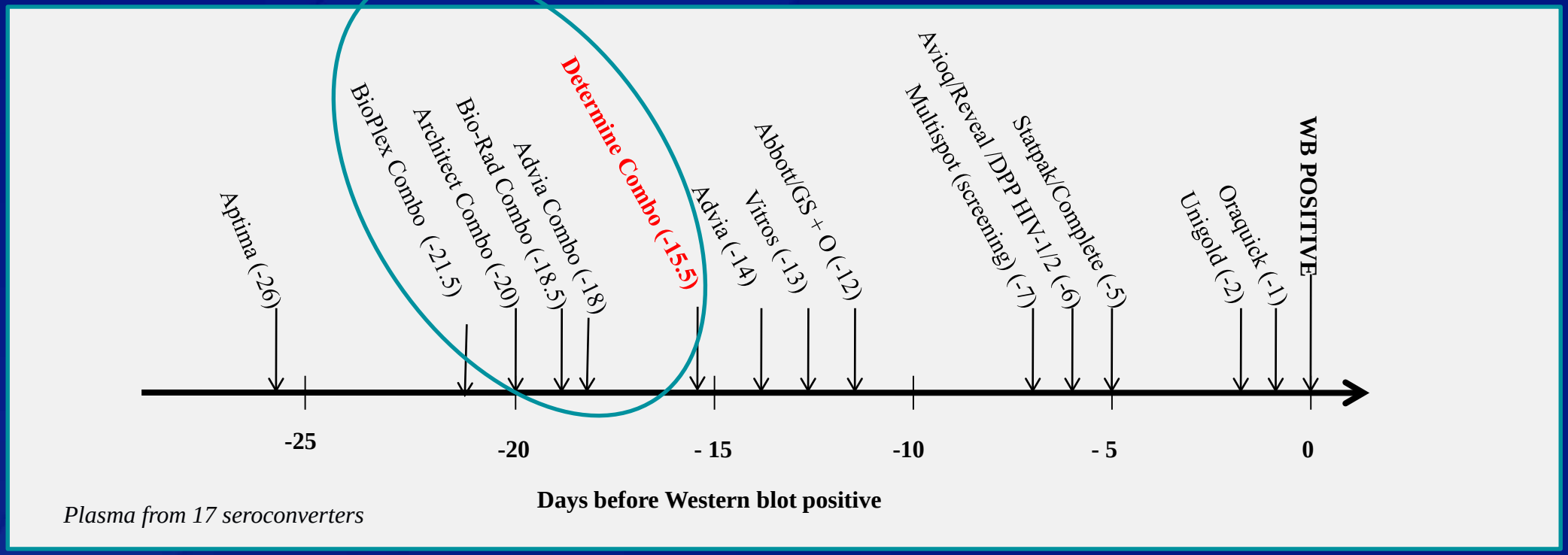
*http://www.fda.gov/biologicsbloodvaccines/bloodbloodproducts/approvedproducts/premarketapprovalspmas/ucm364651.htm

Alere Determine™ HIV-1/2 Ag/Ab Combo (DC)

- Human serum, plasma, and capillary (fingerstick) or venipuncture (venous) whole blood
- CLIA-waived for fingerstick whole blood
- 20 min using 50 µl of plasma/serum/whole blood



DC and CDC/APHL diagnostic algorithm



- Data on performance of DC as a screening test is limited
  - DC detected significantly fewer HIV-1 infections (52.6%) in early stages of seroconversion (38 vs. 20, *p <0.0001*), but showed no difference with established infections
- Results from performance of DC on whole blood from individuals during early infections are inconsistent

Objectives

- To further evaluate the performance of DC as a screening assay in a subset of plasma specimens in the context of the new diagnostic algorithm

- To compare the performance of DC in simulated whole blood to plasma samples from HIV-1 seroconverters

STOP sample set

- **329 plasma specimens collected in San Francisco**
  - Screening Targeted Populations to Interrupt On-going Chains of HIV Transmission with Enhanced Partner Notification (STOP)
  - Multi-site, prospective study evaluating methods to detect acute HIV-1 infections
  - Individuals were tested with FS whole blood with StatPak
  - Plasma specimens were tested with:
    - Abbott ARCHITECT, Bio-Rad Multispot and Abbott m2000 HIV-1 RNA viral load in San Francisco
    - DC at CDC and results compared to previous testing (McNemar's test)
  - Architect-false reactive plasma specimens were tested with Bio-Rad GS HIV Combo Ag/Ab EIA

HIV-1 seroconverters from the US

- **107 selected sequential plasma from 20 commercial seroconverters were used to simulate whole blood samples (40% hematocrit)**
  - Whole blood samples were tested with DC and compared to results from plasma samples
  - DC-reactivity was calculated relative to days after the first Aptima-positive for both sample types

Results

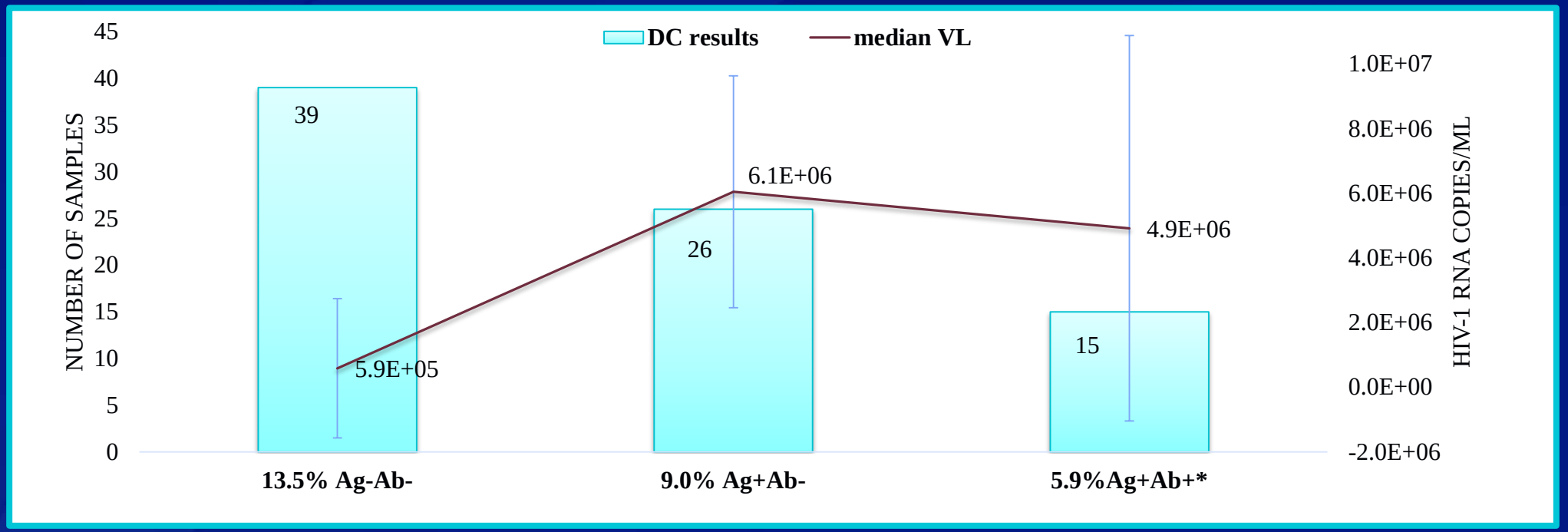
DC performance in STOP specimens

Results from previous testing	total	HIV-1 RNA cop/ml median	Determine Combo results Ag-/Ab-	Ag+/Ab-	Ag+/Ab+	Ag-/Ab+	DC positivity %
ARC-negative/HIV-1 RNA-positive	9	3.49E+03	0	0	0	0	0
ARC-positive/MS-negative/HIV-1 RNA-positive	74	1.65E+06	36	25	8	5	51.4
ARC-positive/MS-indeterminate/HIV-1 RNA-positive	11*	2.33E+06	3	1	3	4	72.7
ARC-positive/MS-positive or-undifferentiated	203**	1.47E+05	0	0	6	197	100
ARC-positive/HIV-1 RNA-negative	32	target not detected	0	0	0	0	0

** 10 and **30 VL results; ARC: Abbott ARCHITECT HIV Ag/Ab; MS: Bio-Rad Multispot HIV-1/HIV-2*

- DC detected 54.1% (46/85) of early HIV-1 infections
  - Difference was significantly different $p<0.0001$
- All established HIV-1 infections were detected by DC
- No reactivity was observed among ARC-false reactive
  - All plasma were non-reactive with GS HIV Combo Ag/Ab EIA

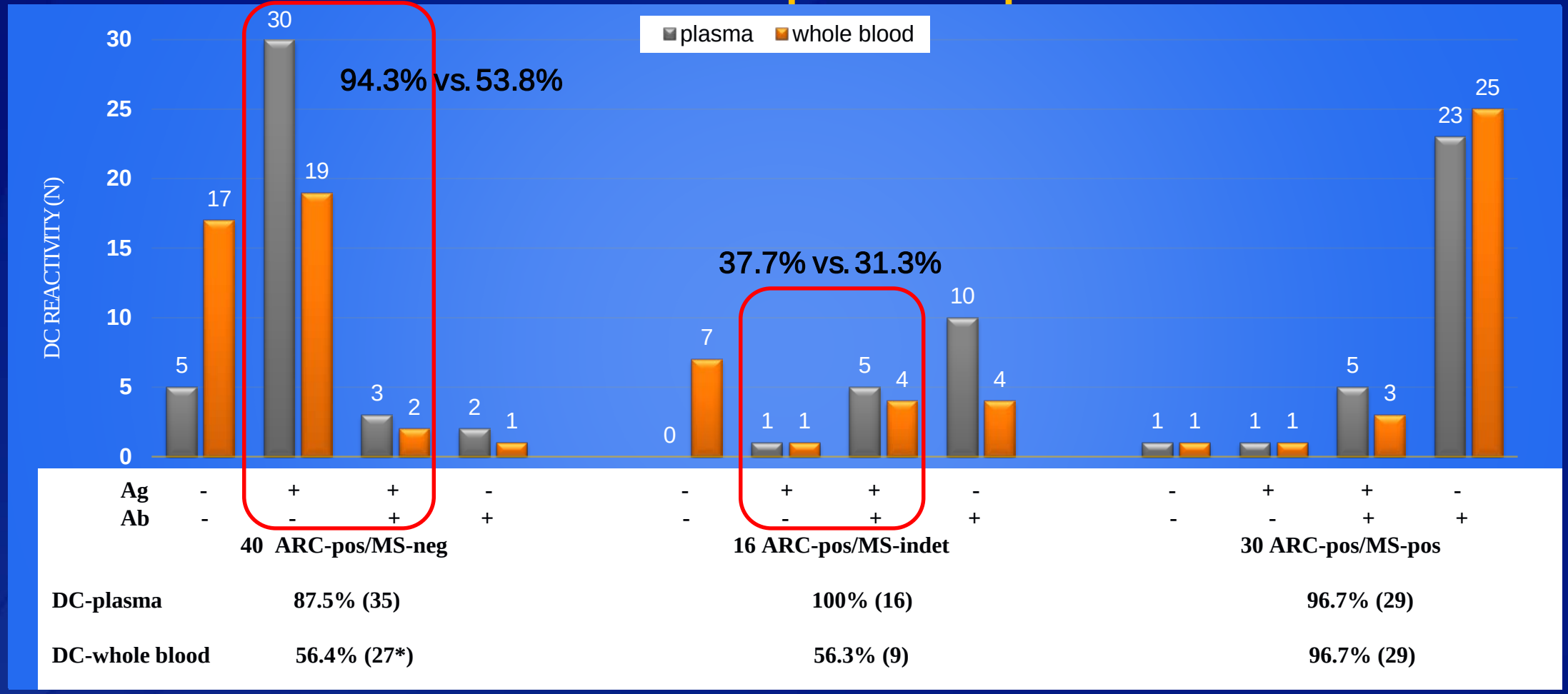
Ag detection among 288 ARC-positive HIV-1 plasma specimens



* 15 of 17 Ag+Ab+ had VL results; 10^7=>10^7 cop/ml: 40= <40 cop/ml; 0=Target not detected

- Among 85 early HIV-1 infections, Ag detection was:
  - 33 of 75 (44.0%) of ARC-positive/Multispot-negative
    - Median VL 4.7x10^6 cop/ml
  - 4 of 11 (23.4%) of ARC-positive/Multispot-indeterminate
    - VL >10x10^7 cop/ml in 3 samples

Marked reduction of Ag detection in early HIV-1 infections with whole blood compared to plasma

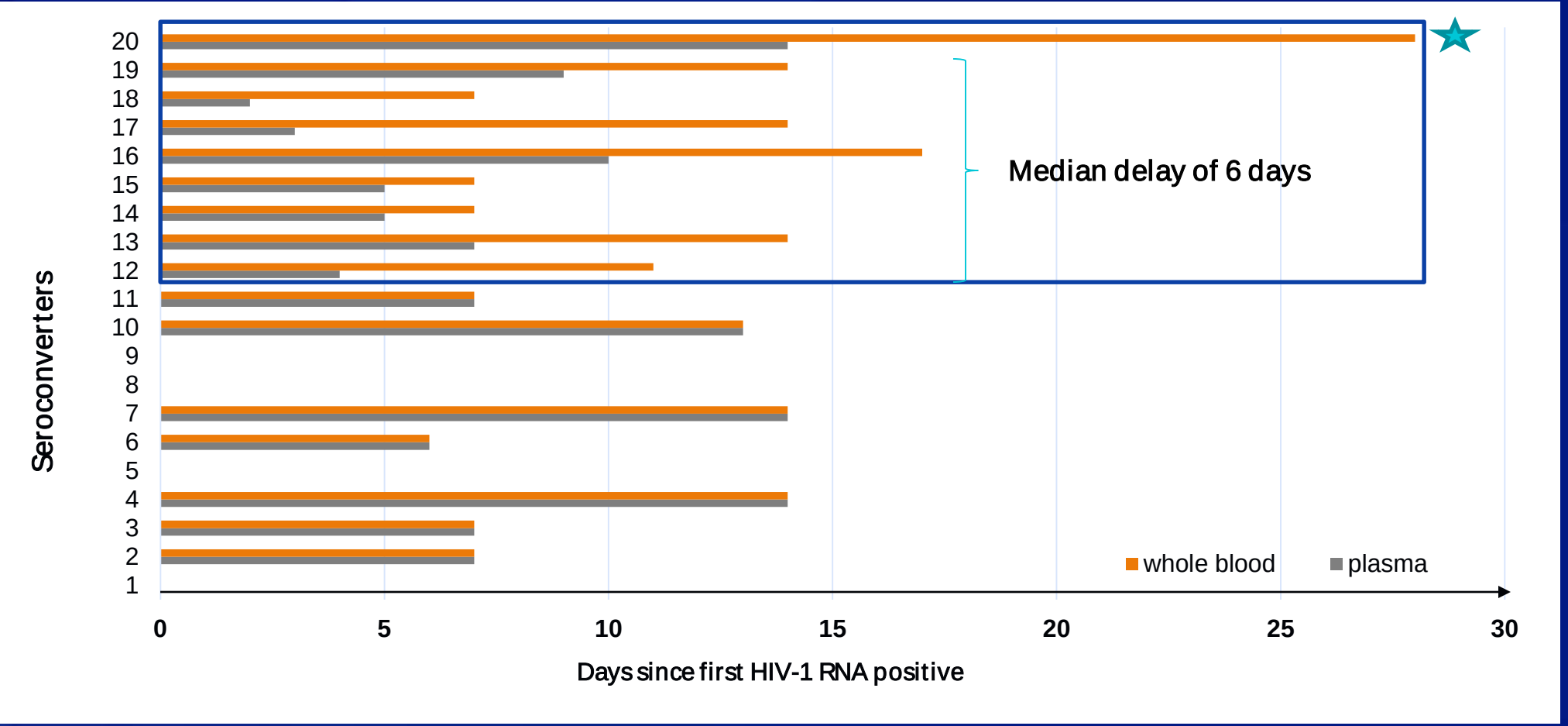


	40 ARC-pos/MS-neg	16 ARC-pos/MS-indet	30 ARC-pos/MS-pos
DC-plasma	87.5% (35)	100% (16)	96.7% (29)
DC-whole blood	56.4% (27*)	56.3% (9)	96.7% (29)

* One whole blood specimen was repeatedly invalid

- Overall DC reactivity in early HIV-1 infections was 91.1% with plasma and 56.4% with whole blood ($p<0.0001$)

Nine of 20 SC showed delayed reactivity in whole blood compared to plasma



- As with plasma, DC with whole blood did not react in 8 samples collected before HIV-1 RNA was detected or in 14 RNA-positive only samples

DC performance with whole blood

- **Initial invalid results were obtained in 17.8% of whole blood specimens**
  - Two specimens that remained invalid after repeat testing were part of a seroconversion panel that never became positive up to 28 days after the first available Aptima positive (no further time points were tested)
- **Eight SC showed a median delay between plasma and whole blood of 6 days**
  - One SC also exhibited a second negative phase with whole blood for 7 days after being Ag+
- **Among 19 SC DC-plasma, the median time of DC reactivity since first Aptima positive**
  - Plasma: 6 days
  - Whole blood: 7 days

Conclusions

- DC used with plasma detected fewer specimens with early HIV-1 infection compared to an instrumented lab-based Ag/Ab assay
- DC with whole blood showed more invalid results than with plasma
- Results indicate that better sensitivity with plasma may be partially due to Ag detection

Considerations

- In this study, simulated whole blood was prepared from commercial seroconversion panels. Further studies will address sensitivity and specificity issues with FS whole blood
- In settings where lab-based testing is not feasible, DC might represent an advantage in detecting HIV-1 infections earlier
- More results are needed to evaluate the performance in the diagnostic algorithm to detect acute HIV-1 infections

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