A Tool for Study of Early HIV Infection

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ABSTRACT

Objective: The Fiebig staging algorithm[1,2] (see Table I below) provides a mechanism for classifying very early HIV infection (within the first three to six months) and for closely estimating HIV infection dates based on a single sample. Using this algorithm, we assembled 24 retrospective samples from 11 recently HIV infected individuals according to the Fiebig stages of each sample into an HIV Early HIV Infection Panel.

Methods: The Fiebig algorithm classifies early HIV infection with HIV RNA, HIV antigen, anti-HIV ELISA and anti-HIV Western blot results. The chart in Table 1 describes the Fiebig stages, the corresponding test results, the average days (with confidence interval [CI]) for each stage, and the cumulative days since infection (with CI).

Results: Retrospectively found serial bleeds and single units from deferred plasma donors were characterized and found to correspond to Fiebig stages Eclipse through V, which describe the course of HIV infection through the first three to five months. Four units representing each of these Fiebig stages were chosen and further characterized with multiple test methods for each analyte. Units chosen to represent the eclipse stage, when no HIV markers are positive, were paired with at least one other unit from the same donor that was at Fiebig stage 1. HIV infection dates are estimated based on the cumulative duration of the highest Fiebig stage from a given donor.

Conclusion: The HIV Early Infection panel provides 24 samples collected from 11 different individuals when each was in the first few months of HIV infection, and their estimated dates of infection. These samples should be useful for those studying early HIV infection, and for those evaluating the performance of test methods for HIV, especially with respect to sensitivity.

FIEBIG STAGES

Table 1. Fiebig Stage Algorithm[1]

Fiebig Stage	Duration of each phase in days (CI)	Cumulative duration in days (CI)
Eclipse	10 (7,21)	10 (7,21)
I (vRNA +)	7 (5,10)	17 (13,28)
II (p24 Ag +)	5 (4,8)	22 (18, 34)
III (ELISA +)	3 (2,5)	25 (22,37)
IV (WB IND)	6 (4,8)	31 (27,43)
V (WB +, P31 -)	70 (40,122)	101 (71,154)
VI (WB +, p31 +)	Open -ended	

INTRODUCTION

Seracare and its predecessor company BBI have been world leaders in HIV Seroconversion Panels for more than two decades.

Plasma donors, who donate twice weekly in the U.S., have been the source of HIV Seroconversions since the first ones were discovered, developed and commercialized in 1986. Plasma donors are permanently deferred from further donation upon being found positive for any HIV marker. Therefore, retrospectively identified series have become shorter in member number and more rare since plasma donors began being screened for HIV RNA in 1998.

Recently, SeraCare has assembled samples from plasma donor units found by analysis of HIV marker test results to be within the first six Fiebig stages (Eclipse through Stage V), and thus likely to be within 0-6 months of their infection date.

These samples are in development for PRB310, an HIV Early Infection Panel.

MATERIALS & METHODS

SeraCare maintains a large, varied, well-characterized inventory of HIV positive plasma units for our control and panel products, and for IVD manufacturers and researchers for their work.

From this inventory, we intended to choose four panel members each from Fiebig Eclipse through Stage V, covering the first 3 to 6 months of HIV infection.

We found that the variability of test methods for HIV markers, particularly HIV RNA and Western blot at the lower extremes of their measurement ranges, meant that the Fiebig stage was sometimes best characterized as intermediate between two stages.

Table 2.

Fiebig Stage	Number of Members
Eclipse	3
Eclipse or I	1
I	6
II	4
III	2
III or IV	2
IV	3
IV or V	1
V	2
Total	24

RESULTS

Table 3.

Member	Donor	Fiebig Stage	Collection Date	Time Elapsed-Prior Collection (days)	HIV1 RNA	HIV Ag	anti-HIV	HIV1 WB
1	Donor A	Eclipse	3/31/2008	0	Neg	Neg	Neg	Neg
2	Donor A	I	4/9/2008	9	Pos	Neg	Neg	Neg
3	Donor A	IV	4/25/2008	16	Pos	Pos	Pos	Ind
4	Donor B	Eclipse	6/29/2009	0	Neg	Neg	Neg	Neg
5	Donor B	I	7/6/2009	7	Pos	Neg	Neg	Neg
6	Donor B	I	7/8/2009	2	Pos	Neg	Neg	Neg
7	Donor C	Eclipse	7/17/2010	0	Neg	Neg	Neg	Neg
8	Donor C	I	7/22/2010	5	Pos	Neg	Neg	Neg
9	Donor C	I	7/24/2010	2	Pos	Neg	Neg	Neg
10	Donor C	II	7/29/2010	5	Pos	Pos	Neg	Neg
11	Donor D	Eclipse or I	7/20/1999	0	not tested	Neg	Neg	Neg
12	Donor D	I	7/22/1999	2	Pos	Neg	Neg	Neg
13	Donor E	II	4/25/2002	N/A	Pos	Pos	Neg	Neg
14	Donor F	II	7/3/2009	N/A	Pos	Pos	Neg	Neg
15	Donor G	II	11/12/2002	N/A	Pos	Pos	Neg	Neg
16	Donor H	III or IV	4/24/2010	0	Pos	not tested	Pos	Neg or Ind
17	Donor H	V	4/29/2010	5	Pos	not tested	Pos	Pos (p31-)
18	Donor I	III	1/22/1997	N/A	Pos	Pos	Pos	Neg
19	Donor J	III or IV	8/13/2001	N/A	Pos	Pos	Pos	Neg or Ind
20	Donor K	III	6/8/2002	N/A	Pos	Pos	Pos	Neg
21	Donor L	IV	9/19/2007	0	Pos	Pos	Pos	Ind
22	Donor L	IV or V	9/21/2007	2	Pos	Pos	Pos	Ind or Pos (p31-)
23	Donor M	IV	9/8/1999	0	Pos	Pos	Pos	Ind
24	Donor M	V	9/22/1999	14	Pos	Pos	Pos	Pos (p31-)

Table 3. Panel members 1 through 24 are each characterized by donor identification, Fiebig Stage, bleed date, time elapsed between bleeds (in days, except where only one bleed from a donor is used), and composite qualitative results of tests for HIV RNA, HIV antigen, anti-HIV, and HIV Western blot. The final panel data sheet will include numeric or quantitative results from several test methods for each marker.

RESULTS

Figure 1. Western Blots results for four donors

Fig. 1a

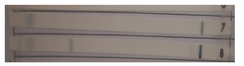

Fig. 1c

Fig. 1b

Fig. 1d

Figure 1a through 1d. Western blot results for sequential bleeds from Donors A (1a), H (1b), L (1c) and M (1d) demonstrate progression of their infections through different Fiebig stages over time.

CONCLUSIONS

- The Fiebig Staging algorithm makes it possible to estimate an infection date and characterize an early infection from a single plasma sample with test results for HIV RNA, HIV antigen, and anti-HIV.
- Panels of samples from very early infection, such as Seroconversion Panels, are becoming increasingly rare, due to improvements in plasma donor screening.
- SeraCare is developing an HIV Early Infection Panel that will contain 24 samples from 11 donors collected in very early HIV infection, and a data sheet that will include results from several methods for each marker and an estimated infection date.

REFERENCES

1. H.Y. Lee et al, Modeling sequence evolution in acute HIV-1 infection. Journal of Theoretical Biology, 261(2009) 341-360.

2. Fiebig, E. W., D. J. Wright, et al. (2003). "Dynamics of HIV viremia and antibody seroconversion in plasma donors: implications for diagnosis and staging of primary HIV infection." AIDS **17**(13): 1871-1879, PMID 12960819.

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