Adding CD4 data to the testing history method

# Goal

To increase the precision of undiagnosed estimates by using CD4 to realistically adjust the probability of infection within infection windows.

# Background

Currently, the testing history method has long infection windows for 1) cases reporting never having had a negative test and 2) cases reporting a long infection window, i.e. a last negative test (LNT) long before diagnosis. Some of these cases may in fact have been infected closer to the time of diagnosis, and this may be reflected in their CD4 and/or viral load. However, experts and the literature suggest that using only CD4 and viral load to predict which individuals were recently infected is difficult to do with acceptable precision. Viral load in particular is highly heterogeneous given the variation in set-point viral load (SPVL) and high loads at the beginning and end of the disease course. SPVL also influences CD4 trajectories. We thus propose to use CD4 data in a manner that allows for population heterogeneity in SPVL.

# Approach

We will use CD4 to create a “CD4 Case” alternative to the Base Case, in which we shift the probability of infection within long infection windows closer to the time of diagnosis when indicated by CD4 count.

This will impact the population TID (time from infection to diagnosis) curve, avoiding the need to do individual-level predictions. Our procedure will also account for the heterogeneity in CD4 levels and trajectories by using infection probability distributions that reflect the degree of variation observed in cohort studies of CD4 trajectories.

## Proposed procedure:

1. Categorize cases with a CD4 count measured within 30days of diagnosis into <200, 200-350, 350-500, and 500+
2. For cases with “long” infection windows (to be defined in bullet #3), place 50% of the probability of infection into the window defined by the median time from infection to the CD4 category. The remaining 50% of infection probability will be distributed between that median time and the end of the infection window (Figure 1). Median times from infection to CD4 category come from two large European cohort studies (1,2) (Table 1). For the >500 group, we will use 1.5 years given the discrepancy between the two studies.
3. A “long” infection window will be defined as 2x or more than the median time from infection to CD4 category. This is because cases with infection windows shorter than 2x the median time will naturally have 50% or more infection probability assigned to that median. For example, under the Base Case, a case with CD4>500 with an LNT 2 years prior to diagnosis would have 1.5/2 = 75% of their infection probability fall within 1.5 years prior to diagnosis. This case would need an infection window of 3+ years in order to have a “long” infection window.

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| **Figure 1.** Change in infection probability distribution for a case with an 18-year window but a CD4 count above 500. 50% of the probability would be distributed across 0-1.5 years prior to diagnosis; the remaining 50% would be distributed across 1.5-18 years prior. |
| 18 years prior to dx  1.5 years prior to dx  Infection window  Base Case  CD4 Case  Infection probability |

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| **Table 1**. Median times from infection to CD4 count | | |
| **CD4 category** | **Years by which ~50% of cases reach lower bound (Ref 1)** | **Median years from infection to CD4 category**  **(Ref 2)\*** |
| >500 | 1.19 | 2.3 |
| 350-500 | 4.19 | 4.17 |
| 200-350 | 7.93 | 7.98 |

\*Based on translating the estimated transition rates between CD4 compartments into median times spent in each compartment

# Expected Impact

There are 3016 cases in 2005-2014 with testing history (59% of the full sample, N=5148). Their breakdown by CD4-count and infection window length is shown in Figure 2. About 10% of these cases that contribute data to the TID would have their infection probability shifted closer to the time of diagnosis under the CD4 Case. There is a slightly higher impact among non-MSM (17%) than among MSM (8%) (Table 3). As a reference point, about 14% of cases contributing to the TID get the 18-year window assumption due to never having had a negative test.

The CD4 Case represents a valuable increase in the precision of our estimates, in terms of our confidence that individuals with long infection windows are being given reasonable infection scenarios. However, the magnitude of impact on the undiagnosed estimates *in this population* will likely be minor. There is greater potential for impact in a population with more individuals reporting never having had a last negative test.

# Time Estimate

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| Program and debug the new CD4 Case | 25h |
| Analyze and present results | 25h |
| Total | 50h |

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| **Figure 2**. Sample sizes and distribution of cases impacted by the proposed CD4 Case. The full sample has N=5148, of which 3016 (59%) have non-missing testing histories. |
| Window shorter than 2x CD4-based median  (N=1882, 62%)  CD4 200-500 and window>16 years  (N=58, 2%)  CD4 350-500 and window>8 years  (N=66, 2%)  CD4>500 and window>3 year  (N=172, 6%)  **Impacted (N=296, 10%)**  CD4 measured within 30d of diagnosis  (N=2178, 70%)  Reported a LNT or No LNT  (N=3016, 100%) |

**Table 3**. Sample sizes and distributions of cases impacted by the CD4 Case, by MSM versus non-MSM, among the 3016 cases with non-missing testing history. Percents are row percents.

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|  | Impacted | | | Not Impacted | |  |
| **CD4>500 and window> 3 years** | **CD4 350-500 and window>8 years** | **CD4 200-500 and window>16 years** | **Window shorter than CD4-based median** | **CD4 within 30d** | **Row Total** |
| MSM | 112 (4%) | 35 (15%) | 24 (1%) | 1487 (66%) | 611 (27%) | 2269 (100%) |
| Non-MSM | 60 (8%) | 31 (4%) | 34 (5%) | 395 (53%) | 227 (30%) | 747 (100%) |
|  | *8% of MSM impacted*  *17% of non-MSM impacted* | | |  | |  |

# References

1. Lodi S, Phillips A, Touloumi G, Geskus R, Meyer L, Thiébaut R, et al. Time from human immunodeficiency virus seroconversion to reaching CD4+ cell count thresholds <200, <350, and <500 Cells/mm3: assessment of need following changes in treatment guidelines. Clin Infect Dis Off Publ Infect Dis Soc Am. 2011 Oct;53(8):817–25.

2. Cori A, Pickles M, van Sighem A, Gras L, Bezemer D, Reiss P, et al. CD4+ cell dynamics in untreated HIV-1 infection: overall rates, and effects of age, viral load, sex and calendar time. AIDS Lond Engl. 2015 Nov 28;29(18):2435–46.