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Monitoring HIV Patients with CD4 Point-of-Care (POC) Instruments: Are Those Technologies Good Enough?

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Antiretroviral treatment roll-out in low-income countries has been relatively successful and covers approximately 25% of the HIV infected population. The target of UNAIDS is to treat 50% of all HIV patients by 2015 [1]. The decision to start treatment of HIV patients is based on clinical symptoms and on the degree of immune deficiency which is measured by counting the number of CD4+ T lymphocytes in peripheral blood. According to current treatment guidelines, patients with less than 350 CD4 cells per µl blood are eligible for antiretroviral treatment [2].

In high-income countries, CD4 counting is performed on expensive high-end flow cytometers with high accuracy and precision. Point-of-care instruments are more affordable than the sophisticated CD4 reference instruments and thus more attractive to settings where resources are limited. Unfortunately, their performance is not always as good and formal minimal performance requirements to validate POC instruments are lacking. Clinicians initiate or change ART based on clinical signs and symptoms, on CD4 counts and on viral load results when available. Therefore, it is important that CD4 results reported by POC instruments are sufficiently reliable to assist clinicians to make the correct decision with regard to HIV treatment.

The CD4 counting performance of an instrument is usually expressed in terms of accuracy and precision. Accuracy is the ability of an instrument to determine the exact concentration of CD4 cells in a random blood sample. Several manufacturers provide their own instrument dedicated CD4 standards as there are no universal CD4 standards available to validate accuracy of the instrument before running patient blood samples. A comparative assessment of the accuracy of different CD4 technologies is therefore difficult to realize. Ideally, CD4 standards should resemble as close as a possible fresh blood sample. Until today, the stabilized (fixed) blood preparations are being used but since blood fixation alters the physical properties of blood, several technologies fail to correctly analyze those samples. Comparison of POC with well-established CD4 instruments is another option, calculating bias between the reference instrument and the POC. However, the measured accuracy of a POC instrument is affected by the (lack of) accuracy of reference instrument. Hence, the measured bias in accuracy is the sum of 2 cumulative errors, one of the POC and the other of the reference instrument.

The precision of a CD4 result, in contrast to accuracy, is relatively easy to assess. This is the ability of an instrument to reproduce the same result, and is calculated by repeating the test a number of times (e.g. 10×). The precision is expressed as percent coefficient of variation (%CV) and is obtained by dividing the standard deviation of the repeated measurements by the mean. CD4 reference instruments have precisions of less than 10%. This means for instance that for most CD4 measurements, the error on the measurement is less than 10%. Several POC instruments are well within the same range as reference instruments but others have larger %CV, up to 30% which could have implications on the judgment of treatment efficacy.

The acceptance criteria for accuracy and precision of POC CD4 instruments should be based, at least in part, on the clinical significance of a CD4 variation due to measurement errors. When a CD4 count is being used to screen HIV subjects for their eligibly for ART and a cut-off of 350 CD4 counts is applied, sensitivity and specificity of a POC technology to correctly identify subjects who require treatment can be calculated. Importantly, in contrast to other diagnostic tests (e.g. HIV serology), a CD4 misclassification of a patient close to the cut-off value of 350 CD4 cells results in delayed treatment or too early treatment but fortunately with little consequences for the patient. Only extreme misclassifications could be considered as potentially dangerous. CD4 counts are also used to monitor ART success and different acceptance criteria may have to be established when POC instruments are used to monitor treatment efficacy. Measurement errors should not be interpreted as immunological failure (declining CD4 counts) and vice versa as such errors would result in unnecessary changes in treatment.

In conclusion, independent and unprejudiced assessment of POC instruments for CD4 counting for use in clinical settings is imperative. The validation of POC requires relevant and realistic acceptance criteria, regardless of their use in settings with limited or unlimited resources.

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