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CD4 immunodiagnostics for HIV in the developing world

This supplement on evaluating CD4 diagnostics for HIV is the fourth in a series of user-friendly operational guides explaining how to conduct evaluations of diagnostic tests for infectious diseases that are of public health importance in the developing world. Here, Andrew Redd and Thomas Quinn introduce the supplement.

The CD4 count, or the percentages of $CD4^+$ T cells for infants and young children, are highly predictive of HIV disease progression, and a significant benefit to long-term survival is observed in patients who begin antiretroviral (ARV) therapy based on higher CD4 levels[1–3]. Traditionally, CD4 tests require fresh whole blood, a reliable cold-transport chain and a flow cytometer. These requirements make determining the CD4 count one of the biggest obstacles to the large-scale implementation of ARV therapy in developing nations. As outlined by Barnett *et al.* in this supplement, the HIV/AIDS epidemic and the subsequent need for high-level laboratory monitoring has driven not only the development of new, simpler flow cytometers, but also improvements in the laboratory-based infrastructure in the developing world. A decade ago, few experts thought that immunological monitoring and ARV care was possible in Africa. Now, nations such as Botswana, Uganda and Rwanda can monitor and treat some, if not all, of their citizens in both rural and urban settings. However, these countries are too often the exception, and the lack of an adequate medical and laboratory infrastructure is still a significant hurdle to the large-scale implementation of ARVs.

To address the shortfall in CD4 monitoring in some countries, the World Health Organization (WHO) amended their recommendations for ARV initiation to allow for the use of the total lymphocyte count (TLC) in lieu of a CD4 count in resource-limited settings[4–6]. However, research from Uganda has demonstrated that the TLC cut-off recommended by the WHO demonstrated poor sensitivity and could not completely replace the CD4 count[7]. This example highlights one issue that is discussed by Stevens *et al.* in this supplement: the urgent need for guidelines to guarantee the accuracy, precision and interchangeability of new CD4 enumeration technologies in the developing world.

The need for accurate patient monitoring is especially important in light of the development of platforms that are more user-friendly than the traditional multi-colour fluorescence-activated cell sorting (FACS) machine. In particular, CD4-specific measurement devices use minimal reagents and increase the sample turnover while at the same time decreasing the end-user costs. Although this is beneficial, these devices cannot be relied on to expand the CD4 monitoring potential to all developing-world environments as laboratory-based processing and testing are still required.

One strategy to avoid the need for a central processing laboratory is to create a mobile point-of-care test. Ongoing research into mobile laboratories and handheld readers is promising, but these devices are either plagued by high initial costs or are not currently available on the market. Additionally, CD4 assays can be greatly affected by the age of the blood sample, which limits their usefulness. The development of blood stabilizers that increase the time allowed from sample isolation to sample processing has helped to alleviate some of the pressure on laboratories to process samples quickly and allowed clinical teams to move into new areas, especially remote rural areas of Africa. However, blood stabilizers can be expensive and are thus usually used exclusively for quality assurance.

UNAIDS estimates that in 2007, approximately 28–30% of eligible adults and 15% of eligible children who were infected with HIV had access to ARVs. In most cases improvements in the abilities of laboratories to determine CD4 counts were pivotal to expanding access. If ARV care is to continue to expand to reach even more patients, new technologies to determine CD4 counts must be designed and deployed rapidly. These new technologies need to be cost efficient, easy to perform and accurate, and should utilize and preferably expand the infrastructure and expertise already in place in the developing world.

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