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The consultation document calls for comments on HIV antigen/antibody tests to help ensure performance criteria are "*appropriate* and support the quality, use and performance" of tests. Assessment of performance for HIV antigen/antibody tests must find an "appropriate" balance between high tests sensitivity and the potential for tests (and the testing models they allow) to enhance the frequency. Given current understanding of the crucial role of undiagnosed HIV and frequent HIV testing among those at risk and acquiring and transmitting HIV, it is crucial the TGA consult widely with laboratory, clinical, public health, epidemiological and modelling experts, along with the community sector, when determining regulations and performance criteria for licensing HIV Point of Care Tests (PoCTs) and HIV self-tests in Australia. As such, we welcome the current consultation document outlining proposed performance criteria for HIV tests.

The key concern arising from the proposed performance criteria for HIV tests is that:

- little justification is provided to support the proposed performance criteria for PoCTs;
- proposed performance criteria appear to exceed those required by international regulatory bodies and potentially do not reflect an "appropriate" balance between test sensitivity/window period and prevention/public health benefit; and
- the proposed performance criteria are likely to represent significant barriers to the registration of new PoCTs and HIV self-tests in Australia and may negatively impact the future role of adapted HIV testing strategies/models in preventing new HIV infections in Australia.

1. PERFORMANCE REQUIREMENTS - PoCTs

2.2 HIV Point of Care Tests (PoCTs)

The TGA acknowledges grounds for a flexible approach to test performance based test "specimen types that are more convenient to the user." (p. 8) The TGA should also explicitly acknowledge the convenience of testing models (e.g., community based and home testing) made possible through PoCTs that may enhance convenience beyond simply the type of specimen used in tests.

It is unclear on what basis the TGA has determined a minimum sensitivity of 99.5% for whole blood and 99.0% for oral fluid. It is unclear whether these sensitivity requirements represent mid-points or lower bound 95% confidence intervals (as might be implied by the terminology "sensitivity of at least …"). If based on lower bound 95% confidence intervals, the TGA's recommended performance

criteria exceed those recommended by the US Food and Drug Administration (FDA) and the Blood Products Advisory Committee (BPAC) (2000, 2009) for PoCTs. The BPAC/FDA recommend a minimum sensitivity of 98% regardless of specimen type. The performance criteria proposed by the TGA are likely to result in PoCTs approved and used for some time in international jurisdictions not receiving regulatory approval in Australia and may dissuade new manufacturers from pursuing registration in Australia. Such an outcome will limit the future role of adapted HIV testing strategies/models in preventing new HIV infections in Australia.

2.3 HIV Self Tests

Similar to concerns relating to 2.2, recommended performance criteria exceed those recommended by the US FDA and the BPAC (2009) for HIV self-tests. Summary documents from the BPAC meeting 16-17 November 2009 (Bethesda, MD) recommended differential sensitivity for weak and strong positive results of at least 98% and 95% (lower bound 95% confidence intervals) in a controlled setting, respectively. In addition, a sensitivity of at least 95% was recommended for an uncontrolled setting (e.g., testing at home). The performance criteria proposed by the TGA are likely to present significant barriers to the future use of HIV self-test kits in Australia.

General statement on performance criteria

While replicating a range of considerations for PoCTs used by international regulatory bodies in jurisdictions where PoCTs have been used to detect HIVfor many years, the TGA appears to have applied more stringent performance characteristics than those used elsewhere. Further, both capillary finger prick and oral fluid specimen collection for HIV testing offer significant benefits over more invasive serological specimen collection and laboratory testing. It is unclear why differential performance criteria are described for PoCTs that use whole blood versus oral fluid specimens other than simply conceding that oral fluid specimens have demonstrated lower sensitivity compared with finger prick.

- Broad consultation with Australian HIV clinical, public health, epidemiological and modelling experts should be used to appropriately justify (in terms of a risk-benefit) performance criteria for HIV tests proposed by the TGA.
- To be judged on a risk-benefit criterion, justification of differential performance criteria based on specimen type needs to include evidence of increased acceptability or oral fluid testing in risk populations and that oral fluid testing may promote HIV testing frequency beyond capillary finger prick.

2. RISK MITIGATION STRATEGIES - PoCTs

In general the risk mitigation strategies proposed for HIV PoCTs and self-testing are reasonable.

The recommendation regarding negative tests associated with risk events that occurred in the past three months and the need for repeat testing is appropriate. However, this point also provides an important consideration for the benefits of PoCTs and HIV self-tests.

It is generally accepted that undiagnosed HIV contributes disproportionately to onward HIV transmission and HIV incidence. At a population-level, however, beyond simply the proportion of people living with HIV that are undiagnosed, it is crucial to consider time undiagnosed when determining the impact of undiagnosed HIV on transmission. Undiagnosed HIV prevalence is a less sensitive indicator of population-level transmission risk than the cumulative time people spend undiagnosed - time that may be spent engaging in risk behaviours, unknowingly putting partners at risk, and not having access the therapies to reduce viral load and onward transmission risk. Reducing the time spent undiagnosed with HIV ultimately relies on increasing HIV testing frequency, particularly among those at high risk of acquiring and transmitting HIV.

Any consideration of the potentially negative consequences of longer window periods and/or reduced sensitivity of PoCTs also needs to consider their impact on HIV testing frequency and the cumulative time someone remains undiagnosed. Even if a false negative result is obtained on a PoCT because of a longer window period, if that PoCT or the testing model it supports increases the likelihood of quarterly or six monthly HIV testing (as recommended by Australian guidelines for high risk MSM), the cumulative time spent undiagnosed may be shortened. However, if standard fourth-generation laboratory testing were used and presentation was within the 15-20 day window period or seroconversion occured shortly after an HIV test, cumulative time spent undiagnosed may be substantial if traditional clinic-based testing present meaningful barriers to retesting.

The above scenario and consideration of current HIV testing frequency among men who have sex with men (see below) should the basis for assessing the risk-benefit of PoCTs and the establishment of appropriate performance criteria. Considerations of the balance between window period/test sensitivity and the frequency of routine HIV test frequency have been reported previously and should be considered by the TGA when determining regulations for PoCTs and HIV self-tests and the setting of performance criteria. For example, recent modelling of the cost effectiveness of routine NAAT HIV testing in the US found that six-monthly fourth generation immunoassay testing delivered increased prevention and economic benefits above 12-monthly NAAT tests, despite improved sensitivity to acute HIV infection associated with NAAT testing (1).

Current low rates of HIV retesting among men who have sex with men (MSM)

In Australia, the HIV epidemic is concentrated among men who have sex with men (MSM). Parameters to consider in understanding HIV transmission risk and prevention in Australia (e.g., background sero-prevalence, prevalence of undiagnosed HIV, risk and HIV/STI testing behaviours) must therefore focus on this population. Most relevant to this consultation is current HIV testing frequency among MSM.

Australian guidelines recommend annual testing for all sexually active MSM and 3-6 monthly testing for "high risk" MSM (2). Although current self-report annual HIV testing among MSM is high (approximately 70% of MSM reporting annual HIV tests (3)), objective clinic data from the Burnet Institute's sentinel surveillance system of high HIV caseload clinics in Melbourne suggests much lower rates of testing among MSM. Recent analyses of MSM testing data from participating clinics (that diagnose over 40% of all HIV infection in Victoria) showed a significant increase in the

proportion of sexually active MSM retesting within 12 months of an index test between 2007 (45%) and 2013 (53%) (4). However this increase in testing is somewhat modest given the significant investment of health promotion focussed on HIV/STI testing among MSM and indicates that approximately half of sexually active MSM are not testing a recommended frequencies. Similar unpublished analyses of six-month return testing data for "high risk" MSM also showed increasing but low levels of return tests inside six months (24% in 2007; 35% in 2013).

To achieve any meaningful decline in the HIV epidemic trajectory in Australia over future years, rates of HIV retesting will need to improve considerably over the rates demonstrated above. Reductions in barriers to HIV testing frequency accrued through the availability of PoCTs are likely to be key improving HIV testing frequency.

3. CONDITIONS FOR APPROVAL

In general the conditions for approval proposed for HIV PoCTs and self-testing appear reasonable.

However, there remains considerable sector concern regarding the ongoing ambiguity associated with the terms "health professional" and the meaning of health professional "supervision". The TGA should be explicit in relation to these terms and their meaning. Given successful trials of community-based and peer-led HIV testing in Australia (and internationally, where the majority of PoCT services are non-clinician led (5)) and the established clinical and laboratory support/referral protocols established in these trials, the TGA should:

- Ensure regulatory approval for operating PoCTs be provided to trained and pre/post-test accredited peer test counsellors who may not have clinical and/or laboratory training or experience;
- Ensure that descriptions of the scope of health professional "supervision" do not pose significant barriers (e.g., requirements for clinical staff to be on site at all times, cost) to the continuation of community-based HIV testing services; and
- Ensure the scope of recent PoCT service implementation experience is drawn upon when considering conditions for approval (e.g., the role of the National Serology reference Laboratory in providing QA/EQAS services, ASHM in the development of training guidelines and curriculum).

While it is acknowledged that regulatory responsibility for some of the above falls with the NPAAC, conditions for test approval stipulated by the TGA should support the above considerations.

4. DEVELOPMENT OF COMPREHENSIVE GUIDELINES

In developing guidelines for HIV diagnostic PoCT applications for inclusion in the ARTG, the TGA should ensure consultation with a sufficient breadth of sector expertise. Ideally, such consultation would obtain advice from: laboratory technicians/researchers, including with specific experience in

the development of PoCTs and PoCT quality assurance; HIV primary and tertiary care clinicians, experts in HIV public health, prevention and epidemiology, experts in epidemic modelling, professionals involved in the establishment of HIV PoCT models in Australia and the community sector.

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