CDCF Advanced HIV Disease Webinar series:
Questions and Answers for webinars on May 27th, June 10th, June 17th, July 1st & July 8th

May 27th Webinar: Questions and answers

COVID-19 and HIV

1. **Hi team, there is a growing anxiety on management of HIV and COVID-19 commodities. Any insight on the possible direction this will take?**

   I *will refer to the PEPFAR Technical Guidance in Context of COVID-19 Pandemic found here: https://www.state.gov/pepfar/coronavirus/, please see section 20. Supply Chain/Commodities, which may address some of these concerns.*

2. **Have any of the African countries implemented HIV self-testing, and what are the opportunities to increase uptake during this pandemic?**

   Yes. Several countries have started this, including PEPFAR-supported sites in South Africa. I will refer to the PEPFAR Technical Guidance in Context of COVID-19 Pandemic found here:

   https://www.state.gov/pepfar/coronavirus/ with key points about HIV-self testing copied below for ease:

CD4

3. **If CD4 is the indicator for treatment starting. How about "test and treat"?**

   CD4 is no longer required to determine ART eligibility. However, whenever available, CD4 should be given to PLHIV newly presenting to care, PLHIV who have disengaged from ART care, and patients who are suspected or confirmed to be failing ART. CD4 testing of these patients allows those who are at high risk of morbidity and mortality from OIs such as TB and cryptococcal meningitis to receive appropriate interventions (such as CrAg testing, TB LAM testing, etc) prior to ART initiation or re-initiation. When carrying out these interventions, every effort should be made to ensure that ART initiation is not delayed unnecessarily.

4. **In resource limited settings, it may not be feasible for maintaining the CD4 testing infrastructure, particularly with scale up of VL testing. Non-availability of CD4 equipment at all sites also leads to delay in ART initiation. In such scenario, will It be not better link advanced disease with good clinical algorithm for screening symptom and signs for identification of probable OI and then subject PLHIV to appropriate diagnosis? Is there a plan for WHO to revise advanced disease criteria?**

   We have seen that with the introduction of test and treat, CD4 has been deprioritised in many settings. This makes diagnosing AHD more challenging. Clinical staging is not optimal as it does not correlate closely enough with CD4. LMIC countries can

diagnose advanced disease, and many still do, by ensuring access to the CD4 in the following situations:

- At initiation of ART
- After disengaging from care
- For patients failing treatment clinically or virologically

Some countries now allow for CrAg testing and TB LAM testing of patients who have a clinical stage 3 or 4 illness, as well as any hospitalized PLHIV, regardless of CD4. These approaches could be considered in scenarios where there is no access to CD4. However, the full benefit of these interventions will not be realized in the absence of CD4 testing.

5. **Will Visitect CD4 strips going to make CD4 POC instruments redundant in future?**

   The Visitect CD4 will hopefully expand overall access to CD4 testing (and package of care interventions) by making testing more feasible at facilities or clinics which currently have no ready access to CD4. However, this does not mean that existing CD4 platforms that are in place will be made redundant. POC CD4 tests which provide a numerical result continue to play an important role in general HIV clinical decision-making.

6. **Do the patients that have the POC CD4 done still need a lab test done or does the facility use the result <200 to request CrAg test**

   This would likely be dependent on country-specific recommendations. The POC CD4 dipstick appears to have good sensitivity and specificity. Ideally, a result of '<200' would indicate a patient for downstream testing with CrAg (and TB LAM depending on symptom criteria) regardless of lab CD4 result. However, since the sensitivity of the POC test is not perfect, there could be value in performing a CD4 lab test for patients with a POC result '>200', where resources allow. Ongoing operational studies are looking into the ideal integration of the POC CD4 dipstick within existing CD4/lab environments.

TB LAM

1. **Is it possible to have a Positive TB LAM test and when the GeneXpert test is negative?**

   Yes. The TB LAM test can be positive even when GeneXpert is negative (or when GeneXpert cannot be done). This is because the TB LAM can also detect extrapulmonary TB, which can be missed by sputum based GeneXpert testing.

2. **To make a case for countries to invest in TB LAM test, is there any evidence coming up on use of LAM in non-PLHIV populations, such as other immunocompromised patients, diabetics etc?**

Not that we are aware of. Currently WHO recommendations for use are specific to HIV-positive patients.

3. **Paediatric TB diagnosis still remains a challenge. Is there a role for use of TB LAM for non-sputum samples for this age?**

   Yes. TB LAM is recommended for use for PLHIV with advanced HIV disease (and certain symptom and clinical criteria) regardless of age. Please refer to WHO guidelines for specific recommendations:

   https://www.who.int/tb/publications/2019/diagnose_tb_hiv/en/

4. **For the LF-LAM assay, are there any interfering substances in urine that may affect the result of the test and does it detect pulmonary or extrapulmonary TB?**

   The urinary TB LAM test detects both pulmonary and extra pulmonary TB, with its ability to detect the latter contributing to a considerable increase in diagnostic yield even when used alongside sputum sample based methods of diagnosis.

   https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5359871/

   It is reported that the anti-LAM antibody, used in the urinary TB LAM test, can undergo cross reaction with some other bacteria, including actinobacteria, candida and non-Tb mycobacteria species, were these to have contaminated the urine.

   https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5427318/

5. **Are there any validations done on TB LAM in children 14 years and below?**
   Yes. Data from these studies is referenced in the latest WHO TB LAM guidelines: https://www.who.int/tb/publications/2019/diagnose_tb_hiv/en/

6. **I think that the diagnosis of DR-TB will be badly impacted by COVOD 19, the transmission will increase and we will have more patients with DR-TB in the coming year especially the HIV positive patients. What do you think about this statement?**
   Data presented during the webinar series has indicated that routine TB testing is decreasing in some countries due to the COVID-19 pandemic.

   Drug resistant TB may develop in a person being treated for TB whose drugs are misused or mismanaged, or who cannot finish their course of treatment. There are some indications of individuals not collecting anti tuberculous medication due to lockdown and so it is possible that this could contribute to an increase in DRTB.

The other main way developing drug resistant TB is being infected by a person who already has drug resistant TB.

https://www.who.int/tb/areas-of-work/drug-resistant-tb/xdr-tb-faq/en/

CrAg

1. **If I am in a setting where I can't access CrAg kits, my patient has severe headache...bit cannot understand their CD4s due to stock outs…what should I do? Try them for CM or refer for CD4 and/ CRAG?**
   If you suspect CM in the absence of CrAg LFA, you can still perform a lumbar puncture followed by India ink testing of the CSF for evidence of cryptococcus. If detected, this patient should be initiated on CM treatment immediately. However, this test has relatively low sensitivity. So if you do not detect evidence of CM, you could consider placing the patient on high-dose fluconazole treatment and referring for a CrAg test (on blood or CSF) if this is available at another facility. Subsequent treatment decisions could then be based on the result of the CrAg test.

2. **Diana asking; in cases where one is unable to do LP due to financial constraints of the patient but with a positive serum CrAg with no signs and symptoms of CCM, what can be the way forward?**
   When an LP is not possible, CrAg-positive patients without symptoms of CCM should be placed on pre-emptive fluconazole treatment. Since CM is not ruled out by the absence of symptoms, this patient should remain in contact with the clinician, and if any symptoms of CM arise the patient should report back to the facility immediately. If LP is still not possible, then the clinician could diagnose and treat for CM based on the positive serum CrAg and presence of symptoms.

Why isn't TB LAM recommended for non-symptomatic outpatients with CD4 between 100-200? Because we know that TB symptom screening is poorly implemented in many settings...

Essentially, sensitivity was higher for <100 than <200 (due to lower sensitivity between 100-200), so the GDG decided not to recommend in that subgroup. That being said, I believe some funders are moving ahead with <200 for all PLHIV to align with the AHD package.

Will PEPFAR be also supporting CD4 testing for baseline and not just for people who will have dropped out and returned to care??

From COP 20 guidance, we have expanded CD4 testing. This is from p.282

"Viral load testing remains the primary method used to monitor the effect of therapy. CD4 testing is supported by PEPFAR in select settings (e.g., at referral facilities) to identify individuals with advanced HIV disease. It is not to be used for determining

eligibility for ART or monitoring response to ART. Individuals ages 5 years and older who have persistent documented viremia despite ART may have a CD4 performed in order to identify those who would benefit from the recommended package for advanced disease. Patients initiating care in geographic regions or populations where the suspected or documented prevalence of patients presenting or re-presenting with advanced disease is >15% either overall or in specific age or risk group may also have a CD4 at initiation of therapy. Finally, if surveillance or public health investigation indicates disproportionately high morbidity or mortality among PLHIV in specific SNUs or populations, or for sites meeting the above criteria of >15% of the population presenting with advanced HIV disease, CD4 testing may be warranted. OU teams should budget for CD4 testing support at high volume facilities implementing advanced disease treatment models.

In addition to centralized CD4 testing, instrument-based point- of-care (POC) testing (e.g., PIMA or Presto) there is an inexpensive, lateral flow CD4 assay that identifies individuals with a CD4 less than 200 cells/mm3 that may be used in the identification of patients with advanced disease when it becomes available and is prequalified by WHO □— this new test can be used as POC or as a near POC test. OU teams supporting CD4 testing should work to optimize their testing networks (if not yet done) to ensure appropriate procurement and placement of conventional, near POC and POC tests, using reagent rental or all-inclusive approaches, as available. Optimization activities should be completed in a step-wise manner and may include: health facility and test location inventories, patient and testing volumes, geospatial maps and/ or calculations of national and subnational test demand versus existing and/ or projected capacity. Priority should be given to testing in conjunction with clinical settings where there is access to the services needed to provide care for individuals with advanced disease."

You mentioned the CrAg SQ and am wondering if you see value in using it at PHC level (because the patient is referred either way to secondary/tertiary facilities for LP and or high dose amphotericin B treatment)?

Yes there could be added value of the SQ titre test at the PHC level. In settings where LPs are not available, or are not carried out (for example due to lack of consent), a high titre SQ result could allow the clinician to know that a patient is at high risk of CM and needs immediate assessment and likely CM treatment, even if that patient is asymptomatic or pauci-symptomatic. In situations where CrAg-positive patients have to be referred elsewhere for LP and potential CM treatment, a titre result could allow clinicians at the referral site to make a treatment decision even if the LP is not done. Additionally, CrAg titre is associated with worse outcomes even in patients who are CSF-CrAg-negative at enrolment and so a clinician may still consider a high titre patient who is CSF-negative for CM treatment, especially if the patient has symptoms of CM.

Could you give an example of evaluations that can be done remotely and how this can be achieved in settings in low- and middle-income countries?

The CrAg LFA and urine TB LAM tests are rapid tests that can be done at the point of care without need for cold chain. This means that they could theoretically be done at almost any level of care, regardless of the facility capacity. Historically, CD4 testing has been the limiting factor in the testing algorithm, as conventional CD4 testing tends to be available only at larger facilities. However, the new POC CD4 dipstick may allow for more decentralized implementation of these interventions. Availability of treatment for TB or cryptococcal antigenemia and/or CM must also be taken into account when considering using these tests at remote or lower level health facilities.

June 10th Webinar: Questions and answers

There were a number of questions in the June 10th Q&A in relation to data which was referenced in relation to people with HIV and TB having a higher risk of death from COVID 19 than those without HIV, those questions are all addressed in the July 1st webinar, which can remains available to view on line.

How should we manage patients with both TB and COVID 19?

We have outlined below the current advice from WHO on this topic which states that:

"In most cases tuberculosis (TB) treatment is not different in people with or without COVID-19 infection.

Experience on joint management of both COVID-19 infection and TB remains limited. However, suspension of TB treatment in COVID-19 patients should be exceptional. TB preventive treatment, treatment for drug-susceptible or drug-resistant TB disease should continue uninterrupted to safeguard the patient's health, reduce transmission and prevent the development of drug-resistance.

While treatment trials are ongoing, no medication is currently recommended for COVID-19 and therefore no cautions on drug-drug interactions are indicated at present. TB patients on treatment should nonetheless be asked if they are taking any medicines, including traditional cures, that may interact with their medication.

Effective treatments to prevent TB and to treat active TB have been scaled up and are in use worldwide. The risk of death in TB patients approaches 50% if left untreated and may be higher in the elderly or in the presence of comorbidity. It is critical that TB services are not disrupted during the COVID-19 response.

Gathering evidence as this pandemic unfolds will be very important, while upholding the norms of professional conduct and patient confidentiality when handling clinical details."

https://www.who.int/news-room/q-a-detail/tuberculosis-and-the-covid-19-pandemic

Any low cost ways to detect cryptococcal meningitis different from the conventional CSF analysis?

The Cryptococcal antigen lateral flow assay can be used on blood or CSF samples and represents an affordable and straightforward way to diagnose cryptococcal meningitis. The approach to diagnosis currently recommended by WHO, according to context, is as follows:

A. In settings with ready access to and no contraindication for lumbar puncture:

i) If both access to a cryptococcal antigen assay (either lateral flow assay or latex agglutination assay) and rapid results (less than 24 hours) are available:

Lumbar puncture + rapid CSF cryptococcal antigen assay is the preferred

diagnostic approach.

ii) If access to a cryptococcal antigen assay is not available and/or rapid results are not available:

Lumbar puncture + CSF India ink test examination is the preferred diagnostic approach.

In settings without immediate access to lumbar puncture or when lumbar puncture is clinically contraindicated:

i) If both access to a cryptococcal antigen assay and rapid results (less than 24 hours) are available: Rapid serum, plasma, or whole blood cryptococcal antigen assays are the preferred diagnostic approaches.

ii) If a cryptococcal antigen assay is not available and/or rapid access to results is not ensured:Prompt referral for further investigation and treatment as appropriate.

https://www.who.int/hiv/pub/guidelines/cryptococcal-disease/en/

How are we planning to manage TB in low developed countries where resources are have been diverted to COVID?

As lockdowns ease in many settings active efforts to detect OIs that may have been missed should be instituted. Integrated diagnostic algorithms for TB and COVID diagnosis; with those presenting to COVID services tested for TB, and vice-versa, in line with WHO guidance

https://www.euro.who.int/en/health-topics/communicable-diseases/tuberculosis/publications/2020/rapid-communication-on-the-role-of-the-genexpert-platform-for-rapid-molecular-testing-for-sars-cov-2-in-the-who-european-region-2020.

How should we manage cryptococcal meningitis patients who also have COVID 19?

While we are not aware of any specific evidence in the management of cryptococcal disease and COVID coinfection, it is important to remember that cryptococcal disease is fatal without appropriate prompt treatment and the presence of suspected or confirmed COVID infection should not delay or impair management of cryptococcal disease. That management should be carried out in hospital and using the best regimes available.

Access to CrAg in Low income countries

Access to cryptococal antigen tests is improving across much of sub-Saharan Africa, with more than a dozen countries now implementing or planning to implement some level CrAg screening as part of routine HIV programming.

https://www.tandfonline.com/doi/full/10.1080/14787210.2020.1785871

For those interested in discussing routine CrAg screening programs, you may contact Noq1@cdc.gov.

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Can you outline any issues in terms of 5FC supply delays?

While some manufacturers have been impacted by lockdown, it is possible to place orders for flucytosine now and we recommend reviewing the information notes that the relevant manufacturers have shared.

Mylan information note

Are there combination diagnostics for SARS-CoV and TB?

There is no combination diagnostic currently available although there is a gene-x-pert cartridge that can be used to test for SARS-CoV-2, the virus that causes COVID-19. This cartridge can be use in the same machines used to test for TB.

How has COVID 19 impacted diagnosis of AHD?

TB case-finding already appears to be suffering. Reports from India suggest an 80% decline in daily TB notifications during the lockdown period compared to the average daily notifications:

http://www.stoptb.org/news/stories/2020/ns20_014.html

In South Africa, there has been a 48% reduction in TB Gene Xpert tests conducted and a 33% decline in positives identified in the 5 weeks following national lockdown on March 27th, compared to the 7 weeks prior. The national institute for communicable disease attribute this primarily to restricted movement and care seeking, given that testing capacity was said to have remained largely intact

https://www.nicd.ac.za/wp-content/uploads/2020/05/Impact-of-Covid-19-interventions-on-TB-testing-in-South-Africa-10-May-2020.pdf

So too the identification of cryptococcal disease, another leading cause of AIDS deaths, has been reported to have declined.

How do we use the existing community structures to screen for advanced HIV disease

Community workers often symptomatically screen for TB. Community workers can also be trained to identify signs of advanced disease and encourage those affected to present to care. Once a person has been identified as having advanced disease, there is also a strong case for proving enhanced follow up support in the community in line with WHO guidance.

What likely measures to adopt to enhance HIV patients attendance to clinic during COVID 19 Lock-down?

It's important that patient messaging makes clear that those with symptoms of opportunistic infections do need to seek care.

For those with a role informing governments, restrictions on movement and transport should be balanced against needs to access care

Where cases may have been missed efforts should undertaken to identify and transport to hospital where necessary, those with undiagnosed opportunistic infections.

How best can we diagnose T.B during the COVID-19 Outbreak

This is a difficult question to answer and will vary from setting to setting. Because of the overlapping symptoms, those presenting with symptoms of COVID, warrant investigation for TB and vice versa. The urinary TB LAM test, used for the detection of TB in AHD, can be used at the bedside and may be of particular use in settings where laboratories are struggling to maintain capacity.

Given the high costs of Liposomal-Amphotericin B & adverse events associated with Amphotericin B deoxycholate, does a 5FC + fluconazole regimen represent a preferred CM treatment option?

The most efficacious regimen demonstrated in the ACTA trial was 1 week of Amphotericin B deoxycholate and flucytosine, this is the WHO's preferred treatment option and if appropriately administered represents the best option for patients. The all oral treatment option of flucytosine and fluconazole offers an effective alternative in settings where amphotericin B cannot be administered (due to stockouts) or cannot be administered safely (due to lack of appropriate monitoring and support).

Why is Amphotericin B recommended and yet liposomal Amphotericin is safer?

While liposomal amphotericin B would be preferable to use, its high cost has limited its use for the treatment of cryptococcal meningitis in low and middle income country settings. Gilead did announce a $16.25 per vial access price but the product is still not accessible at this price in most settings.

Do we anticipate problems with the supply of AmBisome and flucytosine due to the COVID?

Some manufacturers of flucytosine do report capacity issues as a result of lockdown, it is however possible to order flucytosine now. Gilead are manufacturing Remdesivir at the same plant that they have been using to manufacture liposomal amphotericin B (AmBisome). This may reduce their capacity to produce AmBisome.

What strategies can health facilities put in place to ensure effective care for TB and HIV clients in this era of COVID 19

Multi month dispensing of HIV anti-tuberculous therapy can be instituted and extended, as PEPFAR and others are recommending,

https://www.state.gov/wp-content/uploads/2020/04/04.24.2020-PEPFAR-Guidance-During-COVID-19.pdf

(if stock allows and the ongoing supply chain can be guaranteed) to reduce unnecessary clinic attendance, while supporting adherence to therapy. Rapidly switching all DRTB patients to oral regimens, and moving away from more toxic injectable agents, should be prioritised.

Can optimal enhance adherence support be provided in the context of AHD and COVID-19

WHO, UNAIDS and others are recommending multi month dispensing (MMD) where stock allow, so that patients can have medicine supply to hand, even where there are limitations on clinic visits.

For those initiating ART we would still recommend that adherence counselling be provided.

What are the latest medical protocols for CCM management?

From the WHO the most recent guidance is the document "Guidelines for the diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children- Supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection".

https://www.who.int/hiv/pub/guidelines/cryptococcal-disease/en/

The South African clinicians Society 2019 guidance addresses both the use of flucytosine and liposomal amphotericin B as well as providing advice on dose adjustment of therapy.

https://sahivsoc.org/Files/crypto%20guidelines.pdf

What is the proportion of patients presenting with AHD in Malawi?

Answered live: In our clinics approximately 25-30% of patients initiating ART are starting with a CD4 of less than 200. This may be a bit lower in the country average as we are serving populations in referral hospitals which may be a bit sicker than the average.

How are you able to sustain the provision of PPEs to clients?

Answered live: We have just started this in the last three weeks. It is a challenge to keep. We engaged our Community based Organisations to sew cloth masks at reasonable cost as we buy materials for them. We have not saturated all the sites yet but we have started with Centres of Excellence in two sites

COVID 19,TB and acute HIV infection as well other infectious diseases have similar clinical symptoms. what was the steps taken to differentiate before sending a patient for TB screening or HIV testing?

Answered live: We operate HIV Clinics that is integrated with TB. Whether presumptive TB or TB Confirmed cases are done HIV testing as part of case management and again all patients coming for an ART visit have TB symptom screening elicited. We are basically using the WHO case definition A, B and C for COVID-19 and make sure that C is done after ruling out other causes including TB

Is Nutrition enhanced as part of the treatment?

Answered live: Yes, as part of AHD, Nutrition is part of the package. We do nutritional Counselling and provision of nutritional supplements

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How are countries handling stigma associated with COVID-19 affecting TB screening? We have faced problems with a sudden drop in number of presumptive TB cases found with patients being afraid of being tested for COVID-19

Answered live: Yes this is the biggest issue, people are fearful to come to care fearing exposure to COVID-19. Patient education and highlighting that TB is common (at least in high burden settings), TB is curable (if treated) and also highlighting potential risk if undetected. However agree it is a difficult issue driven by fear

So due to this fear they now do not disclose respiratory symptoms?

Answered live: That's a common observation indeed that patients are more likely to under report respiratory symptoms to avoid be associated with COVID -19. In our key messaging, we have included the significance that TB is still there and can have similar symptoms like COVID-19 however, we all know that TB is curable hence we need to manage it. It is true issues of stigma are significant and we just need to work with communities to manage this in our community and public sensitization

Its surely a very serious issue when it comes to TB case notification, but how can we improve on this amidst this raging stigmatizing disease?

Answered live: Yes, this is really challenge during the raging stigmatising diseases. We just need to enhance our public awareness about the symptoms for TB and indeed for COVID19 and then making sure all are aware, and I emphasize the point that TB is curable hence both public health practitioners and HCWs within community and facilities should really coordinate

Yuri, were there patients who were not known co-infected HIV-TBC and then discovered during COVID-19 investigations?

Answered live: I do not have any specific examples of this happening or data to demonstrate the number of times this may be occurring. In a WHO information note (https://www.who.int/docs/default-source/documents/tuberculosis/infonote-tb-covid-19.pdf?sfvrsn=b5985459_18) there are considerations for testing for both TB and SARS-CoV-2 (page 6, point 5). I suspect that the chances of newly diagnosing HIV/TB through COVID-19 investigations will depend greatly on the extent to which programs can build capacity for COVID-19 testing in high TB/HIV burden settings.

In South Africa, do you perform the screening with CrAg just in patients below 100 CD4?

Yes, that is current practice, although the case for screening those with a CD4 count below 200 is currently being reviewed.

My question is how does one clinically differentiate TB and COVID 19 in a vulnerable patient presenting for review and another presenting with COVID infection?

Answered live: Distinguishing TB and COVID-19 can be difficult clinically due to range of symptoms with several that are common to both diseases. Obtaining a careful history is important, though will not always help distinguish. Will be important to continue testing for TB in those you would have tested prior to COVID-19 pandemic. And in locations where

COVID-19 testing can be done, test for those who have applicable symptoms, exposures, or risk factors for severe disease / poor outcomes. Infection prevention practices for those suspected of having either or both diseases will also be very important.

Why do we wait to do TB LAM? We can do it at the first screening if there is a high suspicious of TB. I think waiting to do it later can delay treatment to the patient. Not forgetting sputum as well.

Your point is correct, if you suspect TB, you should perform the urinary TB LAM test immediately. The WHO recommends using LF-LAM to assist in the diagnosis of active TB in HIV-positive adults, adolescents and children with signs and symptoms of TB

Are you saying that TB LAM has to be done to all patients with CD4<200 without signs and symptoms of TB?

In inpatient settings, WHO strongly recommends using LF-LAM to assist in the diagnosis of active TB in HIV-positive adults, adolescents and children: irrespective of signs and symptoms of TB and with a CD4 cell count of less than 200 cells/mm3

Full details of the WHO's 2019 updated guidance on the use of urinary TB LAM can be found here.

https://www.who.int/tb/publications/2019/LAMPolicyUpdate2019/en/

June 17th Webinar: Questions and answers

What should we be doing in terms of scaling up TB case identification post COVID?

This is a good question as the implications of the reductions in case finding observed in South Africa (with similar issues also likely to be occurring elsewhere) is that there may an increased burden of undiagnosed TB in the community at present, which it is important to identify.

The Stop TB partnership recommend the following:

it is important to have supplementary measures and resources to reduce the accumulated pool of undetected people with TB. Such measures may include ramped-up active case-finding, alongside intensive community engagement and contact tracing to maintain awareness of the importance of recognizing and responding to symptoms suggestive of TB, using digital technology and other tools. Securing access to an uninterrupted supply of quality assured treatment and care for every single person with TB will be essential. Notifications will provide a helpful approach for monitoring the progress of such supplementary efforts.

http://www.stoptb.org/assets/documents/covid/Covid%20impact%20on%20TB%20Modeling_Key%20Messages_FINAL.pdf

Role of community healthcare workers in COVID 19 support

Community healthcare workers have been critical to the HIV and TB response. In many settings community healthcare workers are being utilised to track and trace potential COVID 19 cases, although there is a risk that this will divert them from HIV and TB related activities such as TB contact tracing.

What are the access barriers to diagnostics and drugs for Opportunistic Infections

There are many barriers, low perceived demand for some products on the side of manufacturers, high pricing and supply side issues have made many products hard to access, for a more detailed description of some of the particular challenges of accessing flucytosine the following may be useful.

Shroufi A, Govender NP, Meintjes G, et al. Time to embrace access programmes for medicines: lessons from the South African flucytosine access programme. Int J Infect Dis. 2020;95:459-461. doi:10.1016/j.ijid.2020.02.057

Angela Loyse, Françoise Dromer, Jeremy Day, Olivier Lortholary, Thomas S. Harrison, Flucytosine and cryptococcosis: time to urgently address the worldwide accessibility of a 50-year-old antifungal, *Journal of Antimicrobial Chemotherapy*, Volume 68, Issue 11, November 2013, Pages 2435–2444, https://doi.org/10.1093/jac/dkt221

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Diagnosing advanced HIV- How challenging will be it in LMIC countries?

We have seen that with the introduction of test and treat, CD4 has been deprioritised in many settings. This makes diagnosing AHD more challenging. Clinical staging is not optimal as it does not correlate closely enough with CD4. LMIC countries can diagnose advanced disease, and many still do, by ensuring access to the CD4 in the following situations:

- At initiation of ART
- After disengaging from care
- For patients failing treatment clinically or virologically

Thanks Ikwo. please can you speak more of the characteristics of the settings where PEPFAR supports CD4 testing

Answered live: Certainly PEPFAR supports CD4 testing at high volume facilities implementing advanced disease treatment models.

Do patients with clinical stage 1-2 goes positive in CD4 testing? How will this help in diagnosing Clinical stage 1-2?

Studies have shown that a large proportion of patients with clinical stage 1-2 illness will have CD4<200 cells/mm^3. A systematic literature review published in 2014 found the pooled sensitivity of clinical staging to identify patients with CD4<200 to be 73%. A pilot carried out by the Malawi Ministry of Health at 5 health facilities in 2018-2019 found that 58.8% of OPD patients with CD4<200 cells/mm^3 had a clinical stage 1-2 illness. Clinical staging is also poorly sensitive in identifying patients with very advanced HIV disease (CD4≤100 cells/mm^3), even under clinical trial settings.

Munthali C, Taegtmeyer M, Garner PG, et al. Diagnostic accuracy of the WHO clinical staging system for defining eligibility for ART in sub-Saharan Africa: a systematic review and meta-analysis. J Int AIDS Soc. 2014;17(1):18932. Published 2014 Jun 12. doi:10.7448/IAS.17.1.18932

Chisale M. A Pilot Cryptococcal Antigenemia (CrAg) Screening Program Among HIV-Infected Patients in Malawi, 2019.

Hakim J, Musiime V, Szubert AJ, et al. Enhanced Prophylaxis plus Antiretroviral Therapy for Advanced HIV Infection in Africa. N Engl J Med. 2017;377(3):233-245. doi:10.1056/NEJMoa1615822

What does Catalytic Introduction mean?

Answered live : This is a time-limited introduction of a new health product to help countries gain experience on the product with an ultimate objective of having governments and donors continue procurement of this product after the introduction.

How effective is this [visitect] semi quantitative LFA?

There is a publication on this https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7122771/

Answered live: The sensitivity of the Visitect CD4 LFA using venous blood in the laboratory was 95.0% [95% CI: 91.3–97.5] and specificity was 81.9% [95% CI: 78.2–85.2%]. Using FP samples, the sensitivity of the Visitect CD4 LFA was 98.3% [95% CI: 95.0–99.6] and specificity was 77.2% [95% CI: 71.6–82.2%].

what specimen will be use in this test kit? serum or whole blood? thank your answer :)

The Visitect CD4 test uses whole blood

When VISITEC Presented this Semi Qualitative test, it was two types 200 and 350cell/ul. Which one Passed Verification in any country while waiting for WHO PREQUALIFICATION. Do you want to share performance evaluation with Traditional Lab method?

Answered live: The VISITECT Advanced Disease CD4 test is the 200cell/ul version. The review was by an Expert Review Panel for Diagnostics (ERPD) coordinated by the Global Fund.

Technical performance (Manufacturer's submission):

Per Omega, the technical performance compared to BD FACSCalibur is:

Capillary samples: 89.3% sens / 92.3% spec

Venous samples: 86.3% sens / 92.8% spec

An MSF evaluation show higher sensitivity and lower specificity, potentially leading to over-diagnosis of AHD

Capillary samples: 98.3% sens / 77.2% spec

Venous samples: 95.0% sens / 81.9% spec

Is there a plan in policy that will allow self testing for advanced disease just like HIV self test today. would it make sense to advocate for population self testing?

We are not aware of any efforts to develop a self test for advanced disease, although more easily conducted tests for advanced disease may be helpful as they could support the identification of advanced disease in the community. The steps required in the conduct of the visitect test make it less suitable for use by a lay person.

It was mentioned that interim guidance on the use of CD4 Visitect will be available prior to WHO-PQ , how do we get access to this? Will it be provided through the procurement process?

Answered live: The Expert Review Panel for Diagnostics (ERPD) time-limited approval for the test was secured in Q4 2019. The test is now listed as an approved test for procurement by the Global Fund and UNITAID. Some other donors like USAID recognize the ERPD on a case by case basis. However the EMAV is a donation of the initial tests. For more details see:

https://www.clintonhealthaccess.org/unitaid-and-chai-announce-agreement-with-omega-diagnostics-to-increase-access-to-new-portable-cd4-testing-device-for-people-living-with-hiv-in-over-130-low-and-middle-income-countries/

Given that Vistect is no yet WHO prequalified, the countries you support will give special permission to import and use?

A number of countries will grant waivers under varied circumstances. However, we anticipate that the WHO prequalification would be secured later this year, early enough for partners and countries to apply for the EMAV.

The Global Fund Expert Review Panel for Diagnostics (ERPD) have assessed further technical data and improved the rating of the product to risk category 2. This means that the product may be procured with Global Fund and UNITAID resources for a twelve-month period during which it is expected to achieve WHO prequalification.

what is recommendation in high throughput laboratories for CD4 machines?

Answered live: The recommendation is for CD4 network optimization. Country teams should work to optimize their testing networks (if not yet done) to ensure appropriate procurement and placement of conventional, near POC and POC tests, using reagent rental or all-inclusive approaches, as available. Optimization activities should be completed in a step-wise manner and may include: Health facility and test location inventories, Patient and testing volumes, Geospatial maps and/or Calculations of national and subnational test demand versus existing and/or projected capacity. Further details on lab optimization are in the PEPFAR COP 20 guidance. https://www.state.gov/wp-content/uploads/2020/01/COP20-Guidance.pdf

I like the semi quantitative method of CD4 testing, this will improve CD4 testing and therefore early AHD detection

We agree, more details can be found here:
https://journals.plos.org/plosone/article/peerReview?id=10.1371/journal.pone.0230453

For additional information on the VISITECT EMAV please email emav@clintonhealthaccess.org

Zee, has MSF evaluated the cost and outcomes achieved from your mobile program?

Answered live: We didn't conduct an evaluation of the cost or the impact of this intervention but we managed to have a feasibility component of this project and we are still evaluating the patient outcomes for the intervention

Regarding the minimal package of diagnostic AHD tests does this factor in the quality management systems that are needed at the primary care level?

Answered live: Yes, please have a look at this publication
https://www.sciencedirect.com/science/article/abs/pii/S2352301820301016

Can you confirm that VISITECT still needs to be verified in any countries through health sectors?

Answered live: Ideally this is not expected, especially once WHO prequalification process is completed.

Would other PEPFAR Agencies support the use of these POC tools in South Africa, where facilities do have access to lab services but TAT is long due to geographical and patient factors?

South Africa has a comprehensive laboratory network, although point of care tests can still add value, in cases where a rapid result offers particular patient benefit or in rural areas where lab turn around times are longer. The following presentation on point of care technology in South Africa provides some useful considerations.

http://www.samed.org.za/DynamicData/LibraryDownloads/186.pdf

Can early use of Cotrimoxazole reduce mortality rate within 48 hrs of AHD?

The WHO advanced disease guidelines recommend the use of cotrimoxazole for those with a CD4 count ≤350 cells/mm, or clinical stage 3 or 4, or at any CD4 count in settings with high prevalence of malaria or severe bacterial infections.

The provision of cotrimoxazole can reduce mortality from AHD, in terms of the timing of cotrimoxazole prophylaxis, the WHO recommends that "Co-trimoxazole, TB preventive treatment and fluconazole pre-emptive therapy for those with cryptococcal antigenemia should be started as soon as they meet the criteria for the intervention. All medications may be started together.

https://www.who.int/hiv/pub/guidelines/advanced-HIV-disease/en/

Why are we seeing a decline in CD4 testing in many settings?

Following the introduction of test and start we have seen a decline in support for CD4 testing, as well as decline in its perceived importance. It is important to reiterate that CD4 is essential as the main means of ascertaining eligibility for the advanced HIV disease package of care and is important in the following situations:

- *For all individuals commencing ART*
- *For those with clinical or virologic failure*
- *For those who have disengaged from care*

July 1st Webinar: Questions and answers

What are the lessons learnt and best practices to date on maintaining AHD services during COVID?

The WHO has outlined some of the ways that the COVID 19 response may pose risks to the HIV programme, including modelling.

https://www.who.int/news-room/detail/11-05-2020-the-cost-of-inaction-covid-19-related-service-disruptions-could-cause-hundreds-of-thousands-of-extra-deaths-from-hiv

That modelling suggests that the biggest negative impact to the HIV programme will be due to the disruption to ART delivery, and the biggest disruption to the TB programme, from the a reduction in case finding.

Such a reduction in TB diagnosis has already been observed in South Africa, with fewer tests for TB, as well as fewer TB diagnoses during the lockdown period, that in the preceding period.

https://www.nicd.ac.za/wp-content/uploads/2020/05/Impact-of-Covid-19-interventions-on-TB-testing-in-South-Africa-10-May-2020.pdf

In South Africa testing for cryptococcal disease has also declined, a NICD report concluded that:

"COVID-related lockdown measures put in place by the South African government in mid-March have had the unintended consequence of reducing diagnosis of advanced HIV disease and cryptococcal antigenemia. Increased vigilance in laboratory and healthcare surveillance systems will be necessary to detect and respond to any subsequent increase in the development of cryptococcal meningitis as well as other life-threatening opportunistic infections that may result from this."

https://www.nicd.ac.za/wp-content/uploads/2020/06/COVIDImpact_CryptoScreening_2020-06_15-002.pdf

This evidence highlights the importance of ensuring continuity of ART, which can be supported through multi month dispensing (MMD) and ensuring that cases of TB and other opportunistic infections are identified and managed appropriately.

You can find advice from IAS using the following link:

https://www.iasociety.org/covid-19-hiv

CDCF Advanced HIV Disease Webinar series:
Questions and Answers for webinars on May 27th, June 10th, June 17th, July 1st & July 8th

For how long does the TB LAM test remain positive after treatment.

This appears to be variable, although some ongoing positivity beyond 6 months has been noted, in a study where the authors concluded that it may have some utility in assessing response to therapy:

"During anti-TB therapy, the percentage of LAM-positive participants decreased from baseline to 2 months (32% to 16%), and from baseline to 6-months (32% to 10%)"

https://pubmed.ncbi.nlm.nih.gov/25877271/

Community services guidance

The WHO has produced a guidance document entitled *"Community-based health care, including outreach and campaigns, in the context of the COVID-19 pandemic: interim guidance, May 2020"*

They broadly advise that "Existing delivery approaches will need to be adapted as the risk–benefit analysis for any given activity changes in the context of a pandemic. Certain activities may need to be anticipated in areas where COVID-19 transmission has not yet begun, modified where an alternative mode of delivery is safe or temporarily suspended where the risk of COVID-19 transmission is high. Where appropriate, in-person encounters should be limited through the use of alternative delivery mechanisms, such as mobile phone applications, telemedicine and other digital platforms. Specific adaptations will depend on the context, including the local overall disease burden, the COVID-19 transmission scenario, and the local capacity to deliver services safely and effectively."

More detailed advice can be found in the source document.

https://apps.who.int/iris/handle/10665/331975

How do we scale up dual testing for TB and COVID.

Efforts are needed in ensuring continuity of TB diagnosis and treatment, ensuring that fear of disease acquisition does not lead to declines in sputum collection. As lockdowns ease in many settings active efforts to detect OIs that may have been missed should be instituted. Integrated diagnostic algorithms for TB and COVID diagnosis; with those presenting to COVID services tested for TB, and vice-versa, in line with WHO guidance (18) may help.

How do we use the existing community structures to screen for advanced HIV disease?

It's important to train community health workers to be able to identify the those who may have an opportunistic infection and be able to refer those people appropriately.

In settings where CD4 testing is performed at the point of care, this is often carried out in the community, and it's important that when a CD4 result is less that 200 cells/mm3, that they refer the person for appropriate screening and intervention.

what likely measures to adopt to enhance HIV patients attendance to clinic during COVID 19 Lock-down?

Some Public health messaging strategies, while rightly advising those with COVID-19 symptoms to remain home unless severely unwell, should also differentiate and encourage appropriate presentation of those with other diseases.

Is Cryptococcal Meningitis testing routine for HIV positive populations?

Screening for cryptococcal disease (using the CrAg Lateral flow assay(LFA)) is recommended for those with a CD4 count less than 100 cells/mm3, with WHO advising that countries may want to consider screening all those with a CD4 < 200 cells/mm3. Under CrAg screening programs, those suspected of having cryptococcal disease due to a positive blood CrAg result are then tested for CM, with the gold standard for diagnosis being the detection of cryptococcus or cryptococcal antigen in the CSF, also using the CrAg LFA. Even in the absence of routine CrAg screening, patients with symptoms of CM (headache, nausea/vomiting, neck stiffness or pain, confusion, behaviour change, sensitivity to light, fever) should receive blood and/or CSF CrAg testing.

Is Flucytosine FDA approved?

Yes a number of companies including Mylan, strides, and Lupin have FDA approved flucytosine products.

Alternate ways for paying for CM treatment?

In some settings implementing partners are supporting pilots of flucytosine use. It is also though for national programmes to note that flucytosine has been shown to be cost saving (in South Africa) as it allows for the reduction of the hospital inpatient phase of treatment from 14 days to 7 days. (Larson et al, unpublished data)

The Global Fund is also encouraging countries to include advanced disease programming in their applications, see the Global Fund HIV information note.

https://www.theglobalfund.org/media/4765/core_hiv_infonote_en.pdf

What support systems are in place to ensure accessible treatment of Cryptococcal Meningitis in HIV Infected persons in LMIC?

There is a UNITAID-CHAI programme in selected countries to support the roll out of the advanced disease package of care. The Global Fund also encourages countries to include advanced disease commodities in their applications:

https://www.theglobalfund.org/media/4765/core_hiv_infonote_en.pdf

Would poor Nutritional status of HIV+ COVID-19 cases be responsible for higher mortality.

Answered live: Most of the COVID-19 deaths in people with HIV were in people doing well and some were even overweight and so this doesn't seem to play a big role, but it may play a role in some of the patients.

Are there possible benefits from effective and adherent HIV treatment on the outcome of COVID-19?

Answered live: It may be useful to highlight that the risk of COVID and adverse outcomes of COVID is small compared to the risk of other opportunistic infections (such as TB or bacterial infections).
exactly!

In case of Cryptococcal disease and HIV now with COVID19 what should be priority to increase survival of the patient. What will affect the other?

It's important to remember that the absolute risk of death from COVID for an individual patient is low, compared to the extremely high risk of death from cryptococcal disease as well as TB. It is very important therefore that measures to address COVID should not compromise the prompt and appropriate management of opportunistic infections.

July 8th webinar: Questions and answers

What is the yield of CrAg screening test in children

WHO guidelines on cryptococcal screening apply to adults and adolescents, and the decision was taken not to apply the guidance to children given the low incidence of cryptococcal disease in children.

https://www.who.int/hiv/pub/guidelines/cryptococcal-disease/en/

What is the position of PEPFAR on funding the CrAG test?

PEPFAR support the use of the CrAg test, and advises the following in their 2020 Country Operational Plan Guidance for all PEPFAR Countries:

'PEPFAR supports cryptococcal antigen testing, pre-emptive therapy with fluconazole and management of cryptococcal meningitis according to the 2018 WHO guidelines. countries should plan for adequate treatment according to their needs.'

https://www.state.gov/wp-content/uploads/2020/01/COP20-Guidance_Final-1-15-2020.pdf

What is the hook effect and what causes it?

Answered live: Too much antigen or antibody concentration that shields a visibility of Ab-Ag agglutination.

The hook effect occurs when very high concentrations of cryptococcal antigen result in decreased visual intensity of the LFA test lines possibly yielding negative test results.

CrAg may out-compete the gold-labelled antibody-antigen complex that normally wicks up the membrane to interact with the test line which has the immobilized anti-CrAg monoclonal antibodies. The latter reaction will result in a visible test line, but unbound CrAg interacting avidly with the monoclonal antibodies will result in no line. This effect may be negated by changing the dilution of the assay.

[note that while this may be precisely termed a postzone phenomenon the terms prozone is used by many, and is used in the IMMY CrAg package insert.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5869830/

How can we access the CrAg SQ?

Answered live: The IMMY CrAg SQ assay is still in validation studies, but will be available for purchase soon. Another semiquantitative assay called the CryptoPS from Biosynex is available now, although it does not perform quite as well as the IMMY test.

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Are we evaluating any urine based technologies. If yes, How close are we to the possibility of a Urine CrAg LFA SQ that is sensitive and specific

Answered live: We have previously looked at detecting CrAg in urine, and shown that it is reliably detectable. The problem has been that we see a lot of false positive CrAg results in urine using the LFA test. This has stopped it being a useful test in urine. I am not sure if any CrAg test manufacturers are working on overcoming this limitation.

Were the mortality associated with persistently raised intracranial pressure? Or this was not correlated. I ask this question because our experience is that mortality tends to be associated with persistently raised intracranial pressure.

Answered live: Raised ICP is certainly associated with mortality if it is not managed aggressively. In our studies where we do very frequent LPs to manage pressure vert carefully we no longer see an association between raised ICP and mortality.

Is there any role for CrAg SQ in assessing for recurrent Cryptococcal meningitis / treatment failure?

Answered live: I don't have any data on this, but we would expect CrAg to remain positive following successful treatment, and CrAg titre is not useful in assessing treatment response.

Has anyone tried pool testing samples for CrAg screening

we have tried this in the lab and as you can imagine reduces sensitivity by the number in the pool, so have not adopted, but sensitivity would need to be worked out and you would miss possible positives.

How to improve access to Liposomal Amphotericin B + Flucytosine in countries with low incomes?

A difficult question, we need a viable market of affordable products, prioritization of their use by countries and registration. We would encourage everyone to advocate where you are for affordable access to all AHD medicines. see article below for some more thoughts.https://www.sciencedirect.com/science/article/pii/S1201971220301168

So, going forward perhaps for screening, is there a criteria for testing using CD4 count and perhaps for symptomatic treatment if the patients are in a setting where CrAg test cannot be done? Any role for prophylaxis?

The idea of primary prophylaxis is a bit controversial – a Cochrane review essentially found no mortality benefit, and there is the extra cost and risk of driving antifungal resistance with blanket fluconazole. REALITY trial found some mortality benefit, but it did not seem that the mortality benefit was specifically related to treatment for CrAg positive patients. In the absence of a CrAg test, Cryptococcus can still be tested for in symptomatic patients using India ink on CSF specimens. India ink testing has high specificity. However, the sensitivity of this test is much lower than that of the CrAg LFA on CSF. Cryptococcus can also be detected

in CSF culture, but the time to result (1-2 weeks) is generally too long to meaningfully affect treatment decisions.

How can we minimize supply disruptions of ART and antifungals during COVID?

Many countries are currently (as of July 6th 2020) reporting critical levels of antiretrovirals,

https://www.who.int/news-room/detail/06-07-2020-who-access-to-hiv-medicines-severely-impacted-by-covid-19-as-aids-response-stalls

WHO has produced guidance on "**Maintaining essential health services: operational guidance for the COVID-19 context"**

https://www.who.int/publications/i/item/10665-332240

One of the key recommendations is to maintain access to ART through the appropriate use of multi month dispensing (MMD).

How do we tackle challenges of poly pharmacy associated with management of CCM&TB coinfection in advanced HIV disease?

It's important to assess existing medicines with those being commenced for any potential interactions. The issue of pill burden should be addressed in adherence counselling. The fixed dose combination of cotrimoxazole, isoniazid, vitamin B6, fixed dose co-formulation, could help to reduce polypharmacy and may have a role in supporting adherence, but this is rarely used.

What are the updates on cheaper options for CD4 testing? Can patients with advanced HIV also get MMD?

The main benefit of MMD is that is reduces the number of clinic visits necessary for the collection of ART. It's important to remember that under normal circumstances those with advanced disease do need more intense follow up, in their guidelines on managing those with advanced disease they recommend that:

"People with advanced HIV disease require closer follow-up during the initial period of receiving ART to monitor the response to ART and to identify signs and symptoms of possible immune reconstitution inflammatory syndrome. During the REMSTART study, weekly home visits were provided during the first month on ART (46). Even with close initial follow-up in the REALITY trial, many people died at home, with most deaths occurring very soon after ART initiation. People discharged after hospitalization for advanced HIV disease may also require more intensive follow-up. The feasibility of the frequency of visits is context specific and may also depend on the person's ability to travel to the clinical site"

https://apps.who.int/iris/bitstream/handle/10665/255884/9789241550062-eng.pdf?sequence=1

In many settings, eligibility for MMD is dependent upon being clinically stable, in the context of COVID, depending on local conditions, it may make sense to relax guidelines on the provision of MMD, if that will help that a patient does not go without ART. While at the same time ensuring appropriate follow up.

Link to presentations:
https://mailchi.mp/salud.unm.edu/cdc-ahd-previous-session-resources-1555942