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ATIC Newsletter

MAKERERE UNIVERSITY

INFECTIOUS DISEASES INSTITUTE

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INSIDE this issue...

VIRAL LOAD MONITORING

Dr Paul Buyego (MBChB, MMED)

Today, eight million people in developing countries have access to HIV therapy which is a great accomplishment, however, many more people need to be reached with life-saving medicines.[1] The monitoring that goes hand in hand with HIV treatment is still inadequate in these countries.

The tool used for HIV monitoring in resource-limited settings today is a measurement of a patient's CD4 cell count, which does not paint an accurate picture of how a person is responding to treatment.[2]

Studies have shown that the best monitoring tool is Viral load (VL) testing. Viral load is a measure of the number of viral copies a patient has per milliliter of blood. It is a direct quantification of HIV genetic material and an indicator of the status of HIV replication in the body.[1] Frequent VL monitoring aids early

Resistance profile is the gold standard for detection of treatment failure in patients on Antiretroviral Therapy (ART).[3] The more HIV-1 viral particles in blood, the faster CD4+ T-cells are destroyed and the faster the progression towards AIDS.

VL is used routinely in developed countries, but reserved only for limited use in a few developing countries, owing to the cost and complexity. Recently VL monitoring has become commonly used in Africa because it's getting less expensive. Most governments in Africa including Uganda have rolled out annual VL testing.

How are CD4+ T-cell counts and HIV Viral load used?

A CD4+ T-cell count is used, together with the VL test, to ascertain the immune system is fighting the virus. As HIV reproduces within the body, the VL increases and HIV leads to the destruction of CD4+ T-cells and thus lowers the amount of cells present. The higher the HIV VL, the higher the rate at which CD4+ T-cells are destroyed. This indicates that VL monitoring is an early marker to the progress of HIV compared to CD4. However, clinically, there are chances of finding low CD4 and low VLs, stable CD4 with high VLs or high CD4 with high VLs. The goal is to keep VL low and CD4+ T-cell count high.

Why use Viral load and CD4 in monitoring progress of HIV patients

- The number of CD4+ T-cells and virus levels can guide a patient and their doctor in deciding when to start anti-viral treatment.
- Monitoring CD4+ T-cell counts and viral loads during treatment helps the doctor assess how well a patient is responding to their prescribed treatment.
- It helps identify patients who may be having trouble adhering to their treatment and need support.
- It helps identify those that need to be switched to another treatment regimen due to treatment failure caused by the virus' resistance to drugs.

Why viral load is a preferred marker of HIV patient monitoring.

VL is the earliest marker in monitoring HIV progress, hence treatment failure will be detected early.[4] Besides preventing clinicians from leaving patients on ineffective therapy that can lead to drug resistance, it also guides clinicians from unnecessarily switching patients to more expensive drugs.

A patient who is adherent and responds to his/her ART treatment will have their viraemia suppressed within 3–6 months of ART initiation.[5] This is why all patients who have been on ART for at least six months are encouraged to receive a viral load test.

EDITORIAL

Dear Reader,

Greetings from ATIC!

We are glad to be back with yet another issue of the Treatment Information Centre (ATIC) newsletter which is nothing short of exciting and educational!

Viral load (VL) is currently one of the widely preferred measures in monitoring HIV patients' health. In this issue we expound more on VL, its strong points and why it is preferred. Dr Paul Buyego further presents Uganda's position on VL and expounds more on the use of DBS Sampling. To top it all off, you'll find a case scenario; a real life situation in the IDI clinic that will trigger your thoughts on how to cope when faced with a similar situation.

Be sure to check out the latest infectious diseases updates as well as "ASK ATIC" column in which you will discover a ton of insight into VL as thoroughly explored by Joseph Walter Arinaitwe, the learning Innovations Manager.

As we all strive towards a healthy world, we appreciate your input in individual capacities. The ATIC team looks forward to your continued support and hopes to continue receiving feedback regarding the services offered. We can always be reached via email at email queries@atic.idi.co.ug or via the ATIC toll free line 0800200055.

Enjoy this ATIC newsletter issue!

Linda Namara

ATIC Research and Communications

HOW IS VIRAL LOAD MEASURED?

VL testing is done using Reverse Transcriptase Polymerase Chain Reaction (PCR) machines that can utilize Whole Blood, Plasma, or Dried Blood Spot (DBS) samples. The World Health Organization (WHO) has recommended two ways of viral load monitoring, the plasma VL which is the Gold standard and the DBS VL. Most governments in Africa including Uganda have rolled out the DBS VL monitoring because it's cheaper, easy to transport and carries less risks and it's as effective as the plasma VL. However for detecting low VLs, the DBS is less sensitive compared to the plasma VL. For this reason, WHO has set different VL values to interpret treatment failure for the two methods. The plasma VL cut off is 1000copies/ml which is much less than 5000copies/ml for the DBS. Central Public Health Laboratories (CPHL) is responsible for processing all the blood samples in Uganda. CPHL has 2 types of machines which process the samples. The Roche machine is more specific and can detect viral copies up to 20 copies/ml while the Abbot Machine can detect up to 75 copies/ml. Any viral copies below their cutoff value is termed undetectable and the target not achieved or might be specified by numeric values (<20 or <75).

CPHL National Sample Transport system (hub system).

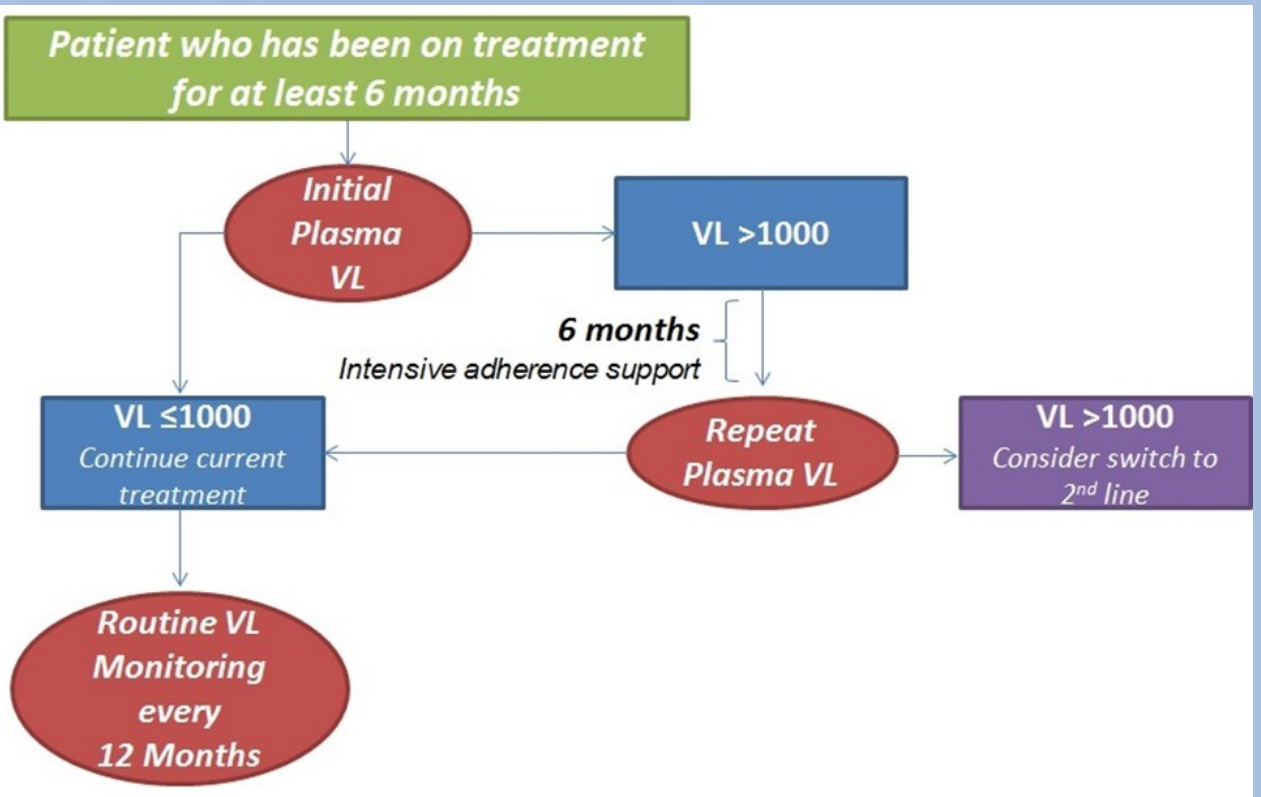
Uganda's position on Viral load.

The Ministry of Health (MoH) is expanding access to VL testing by introducing VL monitoring in a phased manner at select sites. The scale up of national coverage will be done overtime by leveraging the existing National sample transport network and hub system. The program largely relies on DBS samples for VL, with plasma samples (the gold standard) used at those facilities with sufficient resources. The MoH Health has set up a viral load testing laboratory at the Central Public Health Laboratories (CPHL) in Kampala. VL samples are primarily collected as Dried Blood Spot (DBS). However, facilities with cold chain capacity can collect plasma samples.

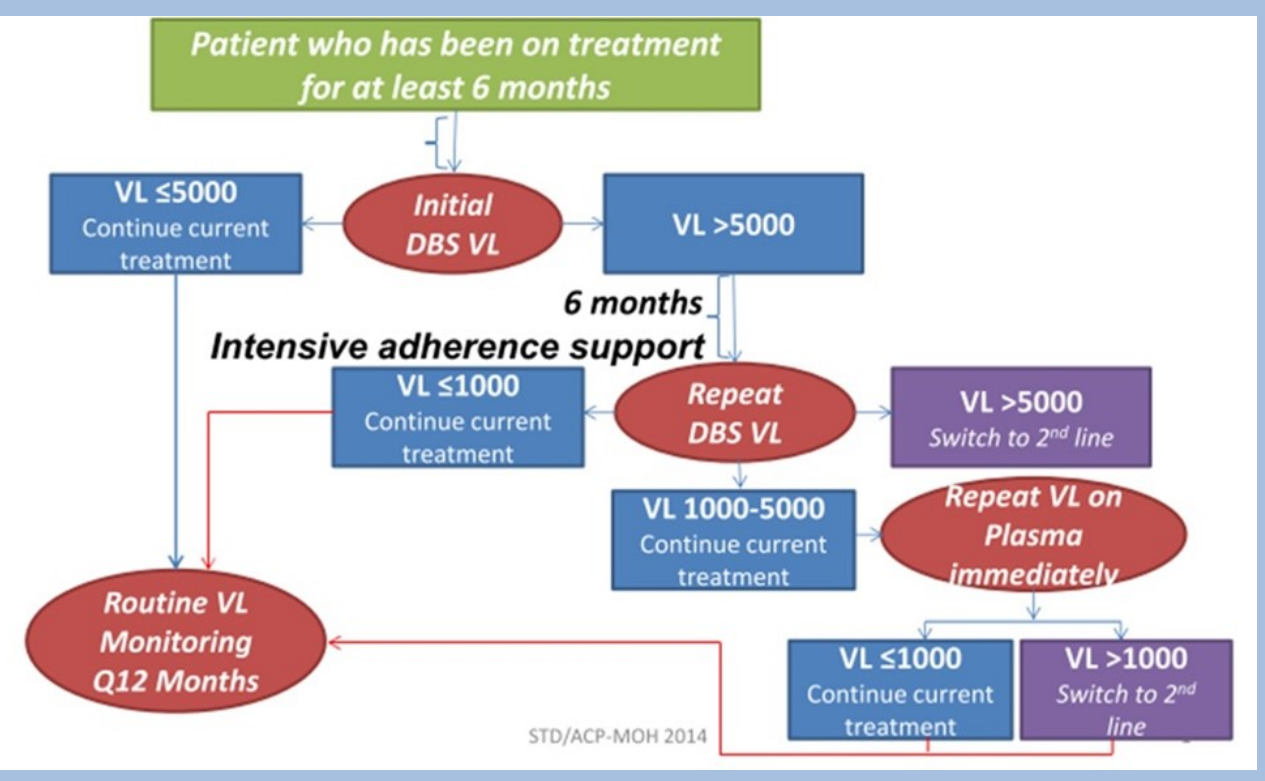
> "IDI is privileged to access plasma viral load and resistance testing."

The VL DBS are transported to CPHL the same way Early infant Diagnosis (EID) DBS are transported by the National Sample Transport Referral Network (hub system). The MoH has developed an algorithm for VL monitoring and interpretation using both plasma and dry blood samples since both methods are used in Uganda as shown by the figures below.

Viral Load Monitoring Algorithm – Plasma (MOH)[2]



Viral Load Monitoring Algorithm – DBS



INTERPRETATION AND ACTION REQUIRED

Using WHO criteria, virological treatment failure is defined as having detectable VL after 6 months of adherence to ART beyond the following set of thresholds:

- Plasma: 1000 copies/ml
- DBS: 5000 copies/ml (adapted to fit Uganda's needs)

Since it is difficult to quantify adherence at the first viral load test, once a patient has a detectable VL they must undergo intensive adherence counseling and have their VL repeated 6 months later. If it is still detectable, such a patient is considered to have virological failure and needs to be switched to second line. Remember that resistance profile is the best way to choose a second line regimen.

WHAT IS NEW?

Optimal viral suppression is defined generally as a Viral load (VL) that is persistently below the level of detection (HIV RNA <20 to 75 copies/mL, depending on the assay used). However, isolated blips (barely detectable VLs following viral suppression, typically HIV RNA <400 copies/mL) are not uncommon in successfully treated patients and are not predictive of virologic failure. Furthermore, the data on the association between persistently low level but quantifiable viremia (HIV RNA <200 copies/mL) and virologic failure is conflicting. One recent study showed an increased risk of subsequent failure at this level of viremia; however, the association was not observed in other studies. The AIDS Clinical Trials Group (ACTG) now define virologic failure as a confirmed viral load >200 copies/mL—a threshold that eliminates most cases of apparent viremia caused by viral load blips or assay variability.

IDI is privileged to have plasma VL and resistance testing services. Using this, IDI is able to follow up patients with low viremia by repeating viral load tests 3 months after intensive adherence counseling. Through this, IDI has observed a few cases with persistent low viremia < 1000copies who later develop resistance. This is not unique as there are a number of studies that have noted this, and groups like ACTG have actually reduced the target level of treatment failure to >200copies. This raises a question on whether the viral load targets for treatment failure need to be revised soon.

IDI is able to follow up patients with low viremia by repeating viral load tests 3months after intensive adherence counseling.

Ask ATIC: FAQs

How often should viral load testing be carried out?

Initial VL is done 6months after initiation of HAART, Then follow up is done annually if patient is suppressed.

I am located in a HC III, can I still get the viral load testing done for my patients?

Yes you can. Currently, the hub system is being used for the transportation of samples to the Central Public Health laboratories (CPHL); the regional referral hospitals are hubs where samples collected and are subsequently transported to CPHL. You should work with your district laboratory focal person (DLFP) to establish the proper transportation mechanism to the hubs. You should also work with your DLFP to ensure that you have the necessary materials for sample collection and transportation.

With viral load testing now available for HIV patients, does this mean that we shall be considering viral load results over the CD4 cell counts?

Viral load testing is a more specific determinant of viral suppression. It gives a clearer picture as to how the ARVs being taken are actually doing their job (arresting viral replication). CD4 cell count is a determinant of immune function and tells us more about disease progression. Both tests are equally important therefore as a health worker it is advisable that you monitor both parameters (CD4 count and viral load).

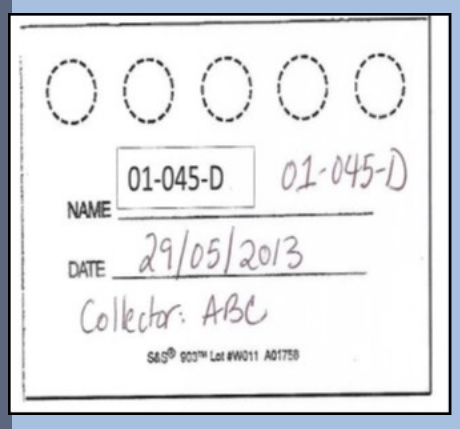
How do we use VL to interpret treatment failure

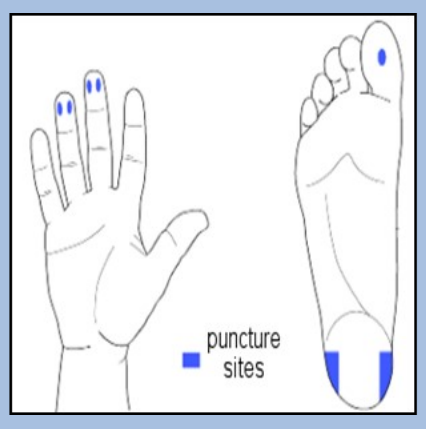
The purpose of taking ARVs is to reduce viral replication, therefore if someone is taking ARVs as recommended, he/she should have an undetectable viral load. Having detectable viral

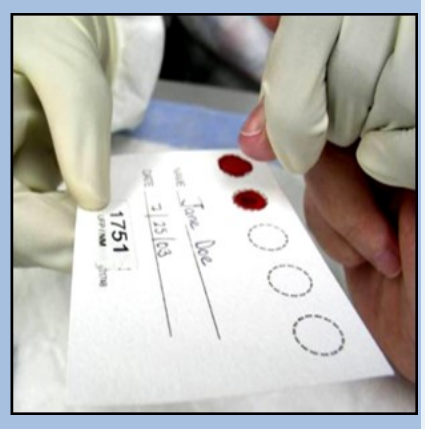
HOW BEST IS BLOOD FOR DRY BLOOD SPOT COLLECTED?

DBS Collection Procedure

1. Review patient information on request forms and assemble supplies.
2. Put on clean powder-free gloves.
3. Label the filter paper with relevant patient information.
4. Select the target site for sample collection.
5. Gently massage the section or warm to increase circulation.
6. Clean the site with the alcohol swab provided.
7. Use the contact-activated lancet to puncture the skin.
8. For toe or finger puncture, apply intermittent pressure on opposite side of site to start blood flow.
9. Wipe away the first drop of blood with sterile gauze.
10. Use a capillary tube provided in the bundle to collect 50µl of blood onto each spot on the card
11. If there are no capillary tubes, allow a free-falling drop of blood to fall onto one of the pre-printed circles on the card. Repeat until all the circles are completely filled with blood.
12. Place the labeled DBS filter papers horizontally onto the drying rack and leave to dry for at least 3 hours or overnight







mean that either the patient is not adhering to treatment or the patient has treatment failure. That is why it is recommended that in case of a detectable viral load, adherence counselling should be done and the viral load test repeated after 6 months. In case the viral load is still detectable after the 6 months of good adherence (specifically a plasma VL above 1000 copies/ml or DBS VL above 5000 copies/ml), this patient has failed on ART and should be switched as soon as possible.

Please note that in the absence of viral load you can still use clinical and immunological criteria to determine treatment failure. In case a client on ART develops a stage 3 or stage 4 event, this is considered to be treatment failure and a switch should be made. If the patient's CD4 is persistently below 100 cells/mm^3 or there is a drop in CD4 to less than 50% of the peak CD4 count or a drop to the baseline CD4 cell count, then this can also be considered as treatment failure and a switch should be made.

HOWEVER

there are some rare cases that are considered a paradox. Some individuals tend to have persistently a low CD4 cell count and yet clinically they are okay and the viral load is undetectable. Under such circumstances, it is recommended that the patient continues with treatment as the ARVs are actually doing their work;

Continues on Page 4

GLOBAL HIV UPDATES

Reproductive health and HIV

In an abstract presented at the CROI conference in 2015, studies showed that Hormonal contraception is used widely and plays an important role in preventing unintended pregnancies and reducing maternal morbidity and mortality. Some (but not all) prospective observational studies have found an increased risk for women to acquire HIV infection when they are using hormonal contraception, especially injectable depot medroxyprogesterone acetate (DMPA, otherwise known as branded Depo-Provera). This injectable contraceptive is a popular contraceptive method, with high use in southern and East Africa, where HIV is prevalent; it is also easy to use, fast to administer, and can be used discretely. Limited data also suggest that HIV infected women using DMPA might be more infectious to sexual partners. The poster discussion at CROI 2015 revealed new information that calls for further discussion and research in this area.

HIV testing and linkages to care, and treatment as prevention

At CROI 2014, one abstract that received considerable media attention was one describing HIV transmission risk in a prospective cohort of European HIV serodiscordant couples on ART (the PARTNERS study). There were no HIV transmissions within the partnerships during the study, translating into an upper 95% confidence interval of the risk estimate of 0.4% per year, and 1% per year for those practicing anal sex. A similar study, among MSM couples primarily from Australia also has demonstrated no HIV transmissions to date (Grulich, abstract 1019LB).

Pre-exposure prophylaxis (PrEP) for HIV prevention

The safety of PrEP was initially established in the clinical trials, and ongoing analyses presented at CROI 2015 reinforced PrEP safety. Both PROUD and IPERGAY found PrEP to be safe in their populations. In addition, several posters assessed aspects of safety. Analyses from the Partners PrEP Study found that PrEP-selected drug resistance detected in 9 participants using 454 ultrasensitive sequencing faded by 6 months following drug cessation (Weis, abstract 983), emphasizing that PrEP-selected HIV resistance, rare to begin with, appears to fade over time. A second poster assessed kidney PrEP safety, finding that the slight decline of 2 mL/min/173m2 in estimated glomerular filtration rate associated with PrEP use disappears within 4 weeks discontinuation of daily oral PrEP (Mugwanya, abstract 981). Finally, PrEP drug sharing was rarely reported (0.003% of visits) or detected based on tenofovir testing when measured in the heterosexual population who took part in the Partners PrEP Study (Thomson, abstract 988).

Encouraging preliminary safety, tolerability and tissue challenge data were presented about the prodrug tenofovir disoproxil fumarate (TDF) ring (Keller, abstract 992LB), which is more potent than tenofovir (TFV) against HIV in vitro and has greater tissue

Ask ATIC: FAQs

...Continued from page 3

suppressing viral replication and you look at other factors that may be causing the low CD4 cell count other than HIV infection itself, like the influence of stress or nutrition, etc

How long will it take before the viral load results can be sent back to us?

It usually takes around 2-3 weeks before the VL results are sent back from CPHL. If you do not get your results, you may contact CPHL and inquire about the status of your results. Always remember to have the details of the sample referral number so that you can be helped.

Interesting Facts...

- World AIDS Day is always celebrated on 1 December. Started in 1988, It is not just about raising money, but also about increasing awareness, fighting prejudice and improving education. World AIDS Day is important in reminding people that HIV has not gone away, and that there are many things still to be done.
- ATIC carries on with learning Innovation by training more health workers online.
- Healthcare workers are thrilled about the timely assistance rendered to them as they tend to patients via the toll free ATIC line.
- IDI presents innovative and cost effective solutions for alumni post-training follow up through SMS at the ASTMH conference.

IDI Contact Information

Website: idi-makerere.com

Facebook: www.facebook.com/InfectiousDiseasesInstitute/

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Reviewed and styled by Linda Namara

IDI Training Department Research and communications

CASE SCENARIO

NBK, 34 year old female is in a discordant relationship with 2 children who are HIV negative. However she also has another partner whose HIV status is unknown. She was ART experienced when she got registered with IDI on 25/06/2010. She has been on AZT/3TC/EFV for 5 years and had a CD4 of 564(21) cells on 13th JUN 2014. She came in for her routine checkup on 16th DEC 2014 to IDI and according to the new guidelines of MOH a blood sample for CPHL Viral Load (VL) and CD4 test was taken. She was clinically stable.CD4 was 525(21) cells and Plasma VL was 840 copies/ul. Following the MOH guidelines on VL, doctors took a decision of repeating the Plasma VL after 1 year while she undergoes intensive adherence counseling. She was enrolled in a study in IDI which took her blood sample for VL on 26th Jun 2015 and VL was 636 copies/ul. Is this treatment failure or suppression? Should we switch her treatment to second line or should we wait and repeat VL after 12 months?

Dr. Arvind Kaimal
MD infectious diseases

Answer:

Viral suppression is achieved by 12 weeks of initiation on antiretroviral (ARV) therapy in patients who have 95% adherence. According to Ugandan guidelines, NBK is suppressed on the first viral load test and we need to repeat her VL test after a year. NBK, having enrolled in a study, had a chance to repeat her viral load 6 months after the first VL test, and the results showed a persistent low viremia despite the adherence counseling that was given. According to some studies, persistent low level viremia may be an indication of treatment failure and is associated with emergence of resistance. Note that in blips, a patient must have had complete VL suppression before alternating with small detectable VLs. NBK was presented in a Switch Meeting in IDI. Switch Meetings are multidisciplinary meetings for medical staff where a suspected patient with treatment failure is presented. This meeting decides whether to switch the patient's regimen and in accordance to physiological and psychological aspects of the patient. Due to persistent low viremia noted in NBK, studies that have associated persistent low viremia with presence of a resistant virus, the meeting decided to switch NBK to TDF/3TC/ATV/r foreseeing possible resistance, however due to IDI's accessibility to resistance testing, a resistance profile was done under an ongoing study on NBK.

Continuing patients on a failing or resistant treatment regimen for a long time will lead to many mutations in the HIV genome which will reduce their susceptibility to other drugs of same class. Example; Being on failed AZT or nevirapine for a long time will lead to the virus being resistant to the other drugs in their respective classes and this will make second line treatment choice difficult as patients may have no backbone treatment.

NBK's resistance profile results came back after the treatment was changed, and she had resistance to 3TC, FTC, EFV and NVP. Resistance profile is a gold standard to detect resistance to ARVs. This will help in confirming resistance and in choosing suitable second line regimen. Due to its cost, it is rarely performed on national basis; therefore, VL is recommended as the preferred approach to diagnose and switch patients in developing countries. Even though the results for resistance profile were not available, NBK was rightly switched to second line without any delay, which prevented more mutations.
CONCLUSION: Viral load is an early mark for detecting treatment failure, and guides in rightfully switching patients early from a failing regimen.

The IDI-McKinnell Knowledge Centre in Makerere University

Wearing a red ribbon is one simple way of showing support to and solidarity with the millions of people living with HIV

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