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Quarterly Newsletter of the AIDS Treatment Information Centre, Infectious Diseases Institute, Makerere University, Kampala

Atazanavir/Ritonavir (ATV/r): The Preferred Protease Inhibitor for 2nd Line Antiretroviral Therapy in Uganda

By: Dr. Brian Ngwatu and Amaan Banwait, CHAI Uganda

Uganda has an estimated 1.2 million people living with HIV and 124,000 new infections a year. By June 2012, 615,000 patients were estimated to be eligible for antiretroviral therapy (ART), while 375,000 were already enrolled on ART.

With an increasing prevalence of HIV in the country, the fear of increased occurrence of 1st line treatment failure is a concern, especially given limited second line (2L) and third line (3L therapy options in our setting. National estimates show that 9,250 adults and 1,264 children are on 2L therapy.

Another concern has been the availability of a 2L regimen that is truly efficacious and safe, readily available, while at same time offering a "user friendly" option for identified patients in need of 2L. Protease Inhibitors (PIs) have been the mainstay of 2L treatment, forming the backbone of many recommended regimens.

Lopinavir/Ritonavir (LPV/r) has historically been the Ministry of Health's (MOH) preferred PI for 2L therapy in Uganda. However, a new PI, Atazanavir/Ritonavir, is now preferable. It is comparable to LPV/r across virtually every dimension, and has lower pill burden and fewer side effects.

In October 2011, the Ministry of Health updated its treatment guidelines to recommend Atazanavir/Ritonavir (ATV/r) as the preferred PI for 2L treatment. ATV/r is now widely available in Uganda and can be ordered from every medical warehouse (NMS, JMS, and Medical Access).

ATV/r vs. LPV/r for 2L Treatment

In choosing ART regimens, key factors have to be considered:

Patient factors	Clinician factors
Efficacy	Availability
Toxicity	Additional requirements for use
Tolerability	Convenience
Convenience	Drug interactions
	Special Patient Populations e.g. children

While LPV/r has been effective for 2L treatment, there are a number of pertinent concerns in line with the above factors such as:

- Side effects (Diarrhea, vomiting, and abdominal pain are some of the most commonly reported)
- The high pill burden (two pills, twice daily) affecting adherence amongst many patients

The Benefits of ATV/r

ATV/r offers the following benefits over LPV/r:

- Comparable efficacy to LPV/r with fewer side effects
- Greater convenience of 1 pill, once-daily dosing vs. 2 pills, twice-daily for LPV/r *(see figure 1 on page 2)*
- Simplified administration can improve adherence
- Recommended by the WHO for use in 2L treatment
- 25% cheaper than LPV/r resulting in significant cost savings

Continued on page 2

Inside this issue:

Editorial

Dear Reader,

On a typical day, ATIC will receive a number of queries from health workers to do with switching of Antiretroviral therapy (ART) for patients under their care. This is expected given the increasing number of patients who are living longer on ART and are bound to develop first line HIV treatment failure. Very often, many health workers are certain of the second line options/regimens but the challenge lies in the availability of the recommended combinations/regimens. Frequent drug stock outs are a common occurrence in most government aided health facilities in Uganda quite often these drugs are available in the national drug warehouses.

In this issue, in collaboration with CHAI we share some of the ways of optimizing ART in resource limited settings. In the first article, the second line PI drug and dosage optimization principle is highlighted and we further explore the role of health workers in optimizing such second line and ART options in our health facilities.

We are glad to share with you related infectious diseases updates from CROI 2013 Atlanta as well as the "OraQuick"-an innovation in HIV testing. In our column on ASK ATIC- which tackles your call center queries, we cover one of the commonest side effects of atazanavir you are bound to encounter in your practice. Please read on and enjoy the information we have specially put together for you.

For a detailed coverage of the references used in this issue email us at ***queries@atic.idi.co.ug****. We too would love to learn from your experiences. Kindly forward your experiences/contributions or feedback to the same email or call us on the toll free 0800200055.*

Ruth Kikonyogo, ATIC Research and Communications

Editorial Committee

Atazanavir/Ritonavir | *Continued from page 1*

ATV/r – one pill, once **LPV/r – two pills, twice daily**

Figure: *ATV/r vs. LPV/r. ATV/r provides the convenience of 1 pill, once-daily dosing vs. 2 pills, twice-daily for LPV/r*

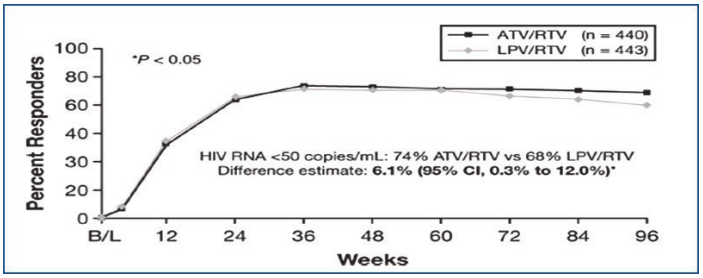
Basing on these benefits, the new MOH guidelines specify ATV/r as the preferred PI backbone for **ALL NEW** 2L patients.

Evidence for ATV/r use

International studies have demonstrated non-inferiority of ATV/r compared to LPV/r, notably the Castle and BMS045 studies, which compared 96 weeks treatment outcome in treatment-experienced and naïve patients respectively.

CASTLE study:

In head-to-head studies with LPV/r, once-daily ATV/r demonstrated comparable efficacy and safety in treatment-naïve patients over 96 weeks:



- Non inferiority of ATV/r was confirmed at 96 weeks
- ATV/r had a better lipid profile and fewer gastrointestinal side effects than LPV/r

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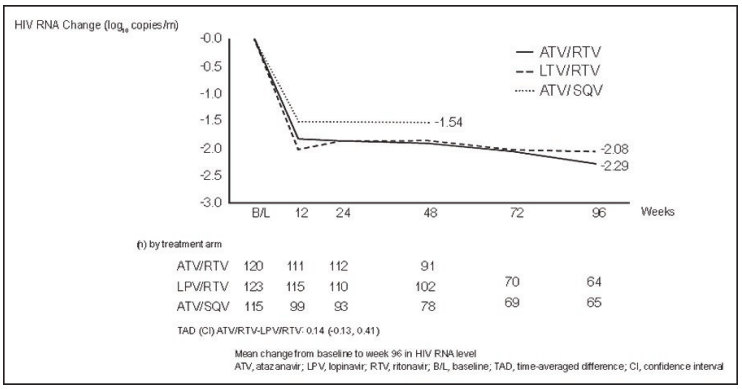
BMS045 study:

ATV/r also demonstrated comparable efficacy to LPV/r in treatment-experienced patients:



Focus Group Discussions in Uganda:

In Uganda, CHAI worked with the Ministry of Health to run focus groups at two facilities (both recognized centers of excellence) to assess patient tolerability of ATV/r in our setting. 29 patients participated in the FGDs in total (15 adults, 14 adolescents). The overall result was that patients overwhelmingly preferred ATV/r to LPV/r. Below are the predominantly mentioned side effects of ATV/r mentioned by the patients:

- **Lower pill burden:** Many patients appreciated the convenience of once-daily dosing.
- **Fewer gastrointestinal side effects:** ATV/r was generally well tolerated with significantly fewer side effects (nausea, diarrhea). A few patients (3 out of 29) reported weight gain as a result of decreased diarrheal symptoms and increased appetite.
- **Jaundice 'yellowing of eyes':** Mild scleral icterus in some patients but the majority of patients will spontaneously improve with time (4 out of 7 interviewed at Mildmay developed jaundice which resolved completely in two of them. One reported recurrent scleral icterus, one reported continued yellow discoloration of eyes). Many patients still prefer ATV/r even if the jaundice persists because of weight gain.

MOH guidelines now recommend ATV/r over LPV/r

	2009 guidelines	2011 guidelines
1st line	AZT/3TC + (NVP or EFV)	TDF/3TC (NVP or EFV)
2nd line	If AZT was used TDF/(FTC or 3TC) + LPV/r * If TDF was used AZT/3TC + LPV/r* ABC + ddI + LPV/r*	If AZT was used TDF/3TC + ATV/r (or LPV/r) If TDF was used AZT/3TC + ATV/r (or LPV/r)

- New patients: "**ALL NEW** 2L patients should be placed on ATV/r if available"
- Proactive switching: "Patients currently on a LPV/r based regimen may be proactively switched to ATV/r" for some reasons like:

Indication	Pre-proactive switching

• Side effects (such as diarrhea) affecting non-compliance and adherence to treatment
• High pill burden affecting adherence to treatment
	• If possible, a patient's viral load should be checked before switching:
	  • <u>If detectable:</u> Patient's adherence and risk of PI resistance should be assessed before switching to ATV/r or 3rd line
	  • <u>If undetectable:</u> Patient can be safely switched to ATV/r
	• If viral load is not available, patient can still be switched to ATV/r at the clinician's discretion

Conclusion

Empirical evidence and economic considerations both favor the use of ATV/r as the preferred Protease Inhibitor (PI) in adult second-line HIV treatment. Major studies include the CASTLE, BMS045, and MASTERS studies internationally.

Currently ATV/r is listed as one of two preferred PI's for use by the WHO and multiple studies have demonstrated that it is non-inferior to LPV/r in both ARV naïve and treatment experienced patients.

A number of factors make ATV/r a better option than LPV/r for most patients on, or identified for, second line antiretroviral therapy. Key factors are comparable efficacy, less toxicity, better tolerability, greater convenience, and less cost.

The Ministry of Health recommends ATV/r as the PI of choice for **ALL NEW SECOND LINE ART** patients. Patients who are stable on alluvia (LPV/r) should continue with the same regime and patients that are not tolerating LPV/r well can be considered for a switch to ATV/r.

For more information, check out page 10 for answers to frequently asked questions about ATV/r.

CLINTON HEALTH ACCESS INITIATIVE

Optimizing Antiretroviral Therapy: Health Workers' Role in Protecting the Second Line ART

By: Arinaitwe Walter Joseph & Dr Christine Kihembo, ATIC

Since the late 1990s, Antiretroviral therapy (ART) has increasingly become available in middle and low income countries like Uganda with a twenty fold increase in ART coverage over the last decade. According to the UNAIDS 2012 report, by the end of 2011, 56% of the population in sub-Saharan Africa in need of ART were actually receiving it. In Uganda, following the nationwide ART roll-out in 2004, the number of people on ART for treatment and HIV prevention is increasing rapidly. Not only are people initiating ART earlier in the disease course in line with the recommended early treatment but also people living with HIV/AIDS (PHAs) are living much longer with ART and therefore the number requiring second line ART is also on the rise.

The significant impact of ART both in the developed world and resource limited settings is well documented with the same ART goals of working towards; maximal and durable suppression of viral replication, restoration and/or preservation of immune function, reduced HIV-related morbidity and mortality and improved quality of life while minimizing the likelihood of viral resistance to preserve future treatment options particularly for those on first line therapy.

Unlike in the developed world where there is access to multiple first line, second line and Salvage ART drug options coupled with widely available routine virological monitoring, feasible phenotypic and genotypic resistance testing; there are very limited options in resource limited countries like Uganda which are also disproportionately affected by the HIV/AIDS epidemic. The number of PHAs in resource limited countries is on the rise and salvage options are not available in the majority of these countries calling for optimization of the available second line ART options particularly for those who require or those who are already on second line ART.

Current ART Situation in Uganda

In Uganda, ART is administered according to the National ART and care guidelines which were updated with the inclusion of prevention of mother to child transmission (PMTCT) in 2012. These guidelines include standard first and second line options of ART based on availability, efficacy and known resistance profile. The second line option is recommended for individuals who have developed resistance to the first line regimens or cannot take the first line regimens due to toxicity/serious adverse drug reactions. With the increased access to and increased time on ART, there has been more frequent development of drug resistance and subsequent treatment failure on first line. The need for second-line regimens has thus become an important issue.

> As the primary source of HIV care... it is our duty to ensure that... medicines are available and managed well.

2nd line ART therapy in resource limited settings like ours is complicated by several factors which include; fewer options for second-line ART regimens, lack of adequate monitoring facilities and difficulty in ensuring long-term adherence due to increased pill burden or meal restrictions. Further compounding the treatment dilemma is the fact that after second line therapy fails; one has to move on to salvage therapy, which is not yet readily available within our setting. For one to benefit optimally from salvage therapy, drug susceptibility testing (DST); which is costly, complicated and not widely available, should be done so that only drugs that can suppress viral replication are utilized to ensure more successful therapeutic outcomes.

Currently, second line therapy is based on protease inhibitors (PI); the preferred regimen PI is Atazanavir/ritonavir (ATV/r) and the alternative regimen is Lopinavir / ritonavir (LPV/r) also known as Alluvia.

ATV/r is preferred because it has a lower pill burden and is administered once daily compared to daily dosing with alluvia *(this has been well covered in the first article of this newsletter)*

The PI is used in addition to 2(two) Nucleoside/nucleotide reverse transcriptase inhibitors (NNRTIs). Commonly used NRTIs in second line ART are AZT if TDF was used in first line ART or TDF if AZT was the NRTI in the first line regimen 3TC is usually maintained the regimen following first line failure due to evidence of increased viral susceptibility to AZT following viral mutations. As we work towards availing more options beyond second line ART options in our settings, it is very important that we protect the few we already have and keep them effective for as long as possible.

This is where you and me, the health workers come in. As the primary source of HIV care with direct interaction with the clients, it is our duty to ensure that these medicines are available and managed well.

HOW CAN WE DO IT?

Optimization of second line ART is best achieved through optimizing first line therapy: i.e. delaying need of second line ART for as long as its beneficial to the patient but at the same time initiating second line therapy at the right time. This can be achieved through the following;

Timely and proper ART initiation

Timely initiation of ART has been showed to give favorable outcomes of therapy in terms of viral suppression and halting disease progression. This means the clients can spend longer on first line therapy and thus will not need second line therapy for a while. This is an effective way of sparing the second line of therapy.

Obviously for one to be initiated on ART; they have been tested, diagnosed with HIV and found eligible for ART. This area has been widely studied with several models and strategies proposed to facilitate early HIV detection and timely ART initiation before major infections that may complicate ART treatment come in.

> Optimizing 2nd line ART is best achieved through optimizing first line therapy... and initiating 2nd line therapy at the right time.

Routine CD4 cell count and clinical assessment should be done for all Pre-ART clients so that you can identify and prepare clients who are ART-eligible early.

It is important to ensure that the client is adequately prepared for ART with emphasis that ART is life-long treatment. Adherence is the second most common predictor to progression of HIV/AIDS and death. Poor adherence is among the major causes of ART treatment failure.

Strategies to encourage pre-ART and ongoing counseling should be comprehensive and reinforced so as to maximize the duration on first line therapy.

The drug regimen used in first line usually influences the choice of second line regimen. As mentioned above, PIs form the backbone of second line ART in Uganda in combination with at least one effective NRTI. The recent evidence of effectiveness of a PI combined with Raltegravir as compared to the current practice of a PI in combination with NRTI in treatment experienced patients will definitely take time to be meaningful in Uganda, given that Raltegravir is currently available only under study settings.

Timely switch to second line

Switch to second line is usually a result of treatment failure and should be done early in order to maximize the potential positive outcome. Early detection of treatment failure will ensure that patients are switched to suitable regimens before the occurrence of multiple mutations affecting second line ART options, and before occurrence of severe clinical events including Tuberculosis which lead to unnecessary switches.

One major strategy for improving the diagnosis of first-line treatment failure in resource limited settings is to increase access to viral load testing. However, due to the absence of regular viral load monitoring, diagnosis of treatment failure might be delayed due to reliance on less sensitive immunological or clinical methods. As costs and technological limitations for viral load testing decrease, its use could beneficially increase switching to 2nd-line therapy while optimizing the duration of first line regimens.

Constraints at the treatment level also negatively affect therapy outcomes. Even in the presence of virological failure, some clinicians may be reluctant to switch to second-line regimens. Some of the commonly featuring reasons of delaying switch to second line ART include; attempts to ensure patient adherence to first line ART, health worker insufficient knowledge and lack of confidence to handling second line ART, myths, among others. Clinicians should therefore decide and decide quickly with the relevant supporting information to expedite the switch.

Early Detection and Proper Management of Side Effects

Side effects are quite common with ARVs. Those that develop with ART initiation usually resolve with time as the body gets used to the drugs in the system. It is important to pass on critical information regarding side effects to your client so that appropriate action can be taken quickly. It is also important to grade the side effects in terms of severity as this may direct the course of action to be taken. For mild and moderate side effects, symptomatic management with close monitoring whilst maintaining the ART may be recommended, while for the severe side effects, stopping ART until the side effects resolve could be an option.

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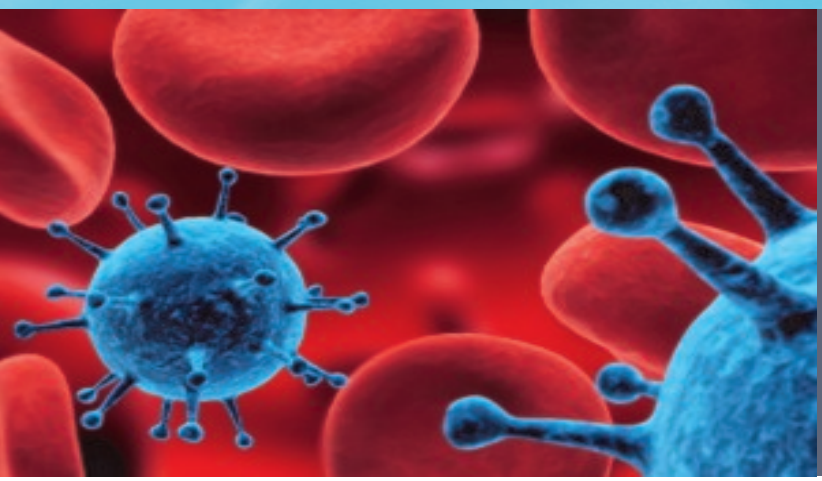


INFECTIOUS

By: The Technical, Research & Communications Team, ATIC

In this edition, we bring to you a summary of highlights in line with the theme: HIV treatment optimisation from the recently concluded 20th conference on Retroviruses and Opportunistic Infections (CROI) held in the month of March 2013 in Atlanta, USA.

HIV/AIDS

Functional HIV/AIDS Cure

One of the highlights that sparked a lot of discussion was a case report of "functional HIV cure" in a previously confirmed HIV RNA PCR positive infant who initiated antiretroviral therapy (AZT/3TC/NVP) 31 hours after birth and continued with LPVr/3TC/AZT after seven days. This baby girl who is currently about 2-5 years old ,was on ART for 15months till the mother discontinued treatment. Not only did she test negative for HIV antibodies and HIV 1 RNA at 18months after being off ART for some time but has also maintained the same results on 4 subsequent HIV RNA tests up to 26months of age. Subsequent Ultrasensitive research blood tests revealed undetectable or hardly any detectable HIV-1 in the baby's plasma, resting or activated purified CD4+ T cells and monocytes at 26 months with no virus in the baby's cells. This has awakened debates regarding whether the infant was really HIV infected or whether the initial HIV tests merely detected virus originating from the maternal blood transfusion occurring at birth.

What seems to be central from this case report and from previous similar discussions and is being universally agreed upon, is the key role that latently HIV infected CD4+ cells play as HIV reservoirs, presenting a challenge in HIV eradication attempts.

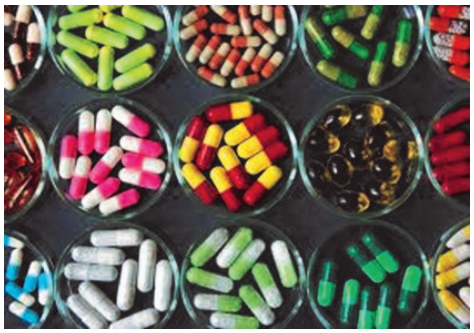
The findings of this report regardless of the side one takes in the debate, is the evident increasing support for early antiretroviral therapy initiation. This could imply full triple ART use instead of a prophylactic regimens for HIV exposed infants and may later have implications regarding acute HIV treatment in adults

Cryptoccoccal Meningitis (CM)

From one of our own Ugandan studies, results of higher incidence of mortality & poorer outcomes in the early ART initiation arm of the COAT study were highlighted. In this study, HIV positive ART naive participants above 14 years of age with the first confirmed episode of Cryptococcal meningitis were randomised to either start ART in the early arm (within 48hours of study entry before hospital discharge during antifungal induction therapy) or in the deferred arm (after 4 weeks after study entry on outpatient basis)

Significantly, there was a lower 6-month overall survival with early compared to deferred ART: 55% vs 70% (P = 0.03), with increased incidence of immune reconstitution inflammatory syndrome (IRIS) in the early arm. It is worth noting that the study was stopped in June 2012 after interim review found substantially higher mortality rates in the early ART arm.

It is against this background that it is now recommended to treat CM first and verifying sterile CSF culture before initiating ART or decreasing fluconazole dose to 400 mg, with ART initiation planned for approximately 4 weeks after CM diagnosis (or 5-6 weeks for patients at greatest risk for early mortality)



Second line ART

One of the HIV treatment highlights at the 20th CROI was news of a nucleoside reverse transcriptase Inhibitor (NRTI) omitting ART regimen proven to be non-inferior to a NRTI-Including regimen in patients failing first line ART starting a new optimized ART regimen.

In this randomized, open-label study, 541 adults with no prior exposure to a protease inhibitor but virologically failing on first line ART were randomised to either receive the WHO standard of care of 2-3NRTI and ritonavir-boosted lopinavir (LPV/r) OR LPV/r + raltegravir (RAL). The primary endpoint was the proportion of participants with a viral load <200 copies/mL at 48 weeks by intention-to-treat analysis.

Diseases Updates

The NRTIs were selected by genotypic testing and the commonly used NRTIs included tenofovir with emtricitabine/lamivudine (TDF+FTC/3TC) (46%) and zidovudine (AZT)+FTC/3TC (18%).

219(81%) participants in the NRTI arm and 223 (83%) in the Raltegravir arm, with a difference of just 1.8 (-4.3-8.7) had viral loads below 200c/ml at 48weeks of follow up. This was not statistically significant p(0.8). Better immunological responses were documented in the Raltegravir arm. This provides a basis and hope for a second line ART alternative regimen in resource limited settings once the Raltegravir that is currently only available in clinical studies is rolled out and becomes widely available.

Tuberculosis (TB)

The news of the possibility of significantly shortening the treatment duration of TB by using higher doses of Rifampicin caused a lot of excitement at this meeting. TB remains the biggest cause of mortality and mortality among people living with HIV/AIDS with the long treatment duration being one of the challenges with resultant high default rates and multi drug resistant TB development on the rise.

In this study, adults with newly diagnosed, uncomplicated, smear-positive pulmonary TB in Cape Town, South Africa were given rifampicin monotherapy from Day 1-7, then rifampicin monotherapy plus standard doses of isoniazid, pyrazinamide, and ethambutol on Days 8-14 and standard TB treatment from Day 14 onwards.

Rifampicin was administered in increasing doses in consecutive groups: Control group: 10 mg/kg 15 among participants, Groups 1, 2, 3, & 4 each with 15 participants were given : 20 25, 30, & 35 mg/kg respectively. Assessments were performed at baseline, Days 1-7, 12, 14 to determine early bactericidal activity, Colony-forming units (CFU) of Mycobacterium tuberculosis on solid medium, Time to culture positivity in liquid medium among other things.

Rifampicin was well tolerated at doses up to 35 mg/kg with few grade 3 adverse events (AEs) and no grade 4 or 5 AEs. Analysis of CFU decline over duration of therapy did not show substantial change in slope following addition of isoniazid, pyrazinamide, and ethambutol but there was a trend toward greater early bactericidal activity with increasing rifampicin dose. If this is further studied and is translated into practice it would be a great stride in the fight against the big killer TB.

References

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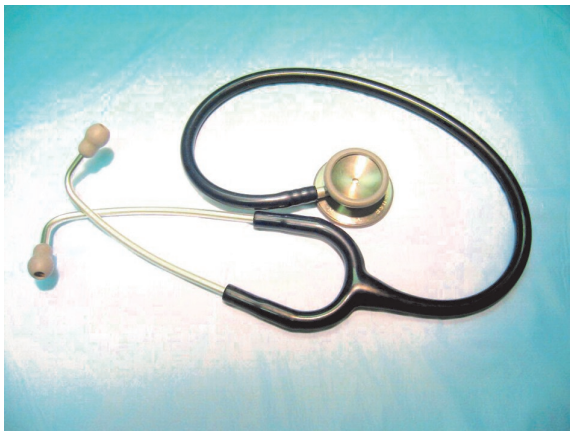
Proper management of these side effects can have a bearing on the effectiveness of the first line therapy thereby preserving the second line. Adverse reactions to ART such as skin drug reaction are common with NNRTIs like NVP.

Some side effects may affect the treatment outcome indirectly by influencing a client's adherence thereby leading to drug resistance and subsequent failure. Darkened nails may not mean much to a health worker but may mean so much to a young woman who is very conscious of her beauty. Therefore, as a health worker, do not take any side effect lightly no matter how minor it may appear to you without understanding a client's perception as it can impact the therapeutic outcome if not realized and dealt with accordingly. It is important to give your clients adequate information of the expectations and reassure them of the value of ART and importance of appropriate side effect management.



Proper Adherence Monitoring and Early Identification of Potential Failure

It is very important to monitor your clients on ART regularly. Routine CD_4 counts and where possible viral load testing should be done. Viral load is a more accurate monitoring parameter as it measures the effectiveness of the regimen in use. The primary function of ART is to suppress the virus allowing immune recovery to occur. Therefore in optimal ART, viral loads are expected to be undetectable. However in the absence of viral load testing, regular immunological monitoring (six monthly CD_4 testing) in addition to clinical monitoring is recommended. Clinical monitoring is the bare minimum for every patient on ART.

Adherence monitoring is also a vital aspect. It is mainly done through pill counts and self-reports in resource limited settings. Good adherence is critical for effective ART. Poor adherence is the commonest single predictor of ART failure. Poor adherence on first line is likely to translate into poor adherence on second line ART given that second line ART usually has a higher pill burden and more discomforting side effects. Counseling prior to switch to second line therapy is critical in addition to addressing identified issues that contributed to poor adherence to first line therapy. You need to closely monitor your patient's adherence to minimize scenarios of resistance and failure.

Proper Stock Management: Timely & More Accurate 2nd Line Client documentation

This is mainly for purposes of forecasting and quantification of the drug logistics necessary to sustain second line ART within the facility. One of the biggest threats to effective ART is facility ART stock outs.

To put this into perspective, every one in eight of the ATIC inquires is seeking for treatment alternatives following stock outs. It is not uncommon that we have reports of ART drugs expiring with in the medical ware houses amidst stock outs of the same drugs with in the health facilities .

Frequent drug stock outs make clients lose trust in the health system, affect adherence and definitely lead to unfavorable outcomes. It is therefore your duty to ensure that enough drugs are ordered for to ensure sustained supply to all clients whether on 1st line or 2nd line ART.

At the end of each reporting period, it is important to know the number of new second line clients enrolled during the period as well as the ones you expect to enroll soon. Submitting this information in time and incorporating it into the orders for ARVs made will have a positive impact on the logistics management. Making adequate orders is just one of the aspects of proper stock management. Other considerations include adequate storage facilities to maintain drug potency, adequate disposal of expired drugs to mention but a few.

To achieve adequate stock levels, proper stock monitoring is paramount and appropriate records should be maintained (stock cards, dispensing logs, etc.) so as to have the right information to use when time to place orders for ARVs comes.

To overcome some of the challenges encountered in the drug supply chain system in the country, innovative ideas are being devised and will soon be ready for roll out. For this update watch out for the next edition of our newsletter.

Conclusion

Despite many challenges, there are certain practical day to day strategies that health workers can adopt for better ART management. The current second line antiretroviral therapy can remain effective and relevant to the treatment setting provided we the health workers do our part and do it to our best.

The Over the Counter Oral Fluid HIV Test Kit: Is it the way to go for Uganda?

By: Eva Laker, Pharmacist & Logistics expert, PCT IDI and Dr. Christine Kihembo, ATIC

An oral swap of saliva from the comfort of your living room and *Walla....* you could know your HIV status in just a few minutes. Sounds so simple and appealing, right?! Why then did the recent media news of availability of over-the-counter oral HIV test in Uganda cause significant debates with the public demanding Ministry of Health's standpoint? Similarly, the approval of the new, non-invasive oral home test for HIV called "OraQuick" has not been very simple and still has a lot of implications in the HIV/AIDS control struggle. In resource limited settings like Uganda, more than a third of the population do not know their HIV status, continue the risk of HIV transmission and many people still present late for HIV/AIDS care. Yet we know that early HIV diagnosis, linkage to care and subsequent initiation of highly active antiretroviral therapy are some of the proven approaches to reducing HIV transmission and optimizing HIV care.

Innovations in HIV diagnostics that would facilitate rapid, accurate and less invasive with zero risk of occupational HIV exposure HIV tests would be a big positive step in reducing HIV transmission.

Rapid HIV testing forms the cornerstone of HIV diagnosis in the developing world where confirmatory viral PCR testing is seldom done.

OraQuick approval and rollout

The OraQuick test, manufactured by OraSure Technologies, obtained its initial approval as an HIV-1 finger stick whole blood test in 2002. Since 2004, the test has undergone modifications to include HIV-2 detection and HIV antibody detection on plasma and oral fluids. The OraQuick HIV test was subsequently released and recommended for use by trained medical personnel with high sensitivity and specificity rates of 99.3% and 99.8%, respectively. As expected, the test has found its way into the common man's reach; however, its use by the public does raise concern about the probable, unintended consequences.

> ... a systematic review [showed that] the OraQuick test had a high positive predictive value... in high HIV prevalence settings.

Utility of OraQuick in the developing setting

During a second phase clinical study among a population with low HIV prevalence, the OraQuick HIV test was applied in the setting of untrained users. Results showed the sensitivity and specificity were similar to tests run by trained medical personnel at 97.9 and 99.79%, respectively, which was promising.

During the third phase clinical study that looks at how the test would be used in a real-world setting, sensitivity dropped to 92.9% while specificity remained high at 99.8%. There was no clustering according to sex, literacy level, gender or sexual orientation for subjects with false negative results. The results imply a possibility that 1 in every 12 HIV positive individuals will test negative while using this test. This drop in sensitivity is of particular concern for populations with high HIV prevalence; a test with the highest detection potential is desirable to detect as many infections as possible to hopefully halt further HIV transmission.

However, in a systemic review and meta-analysis of HIV rapid tests, the OraQuick test had a high positive predictive value when used on oral fluids from individuals from high HIV prevalence settings. Similarly, field comparison of rapid tests in Zambia, a country with a high HIV prevalence of 15% at the time of the study, greatly recommended the addition of the OraQuick test into the national testing algorithm despite a significantly high cost involved. Moreover, the test was shown to be very feasible for round-the-clock rapid HIV testing in a crowded labor ward in India, providing an easier and faster opportunity for the detected HIV positive mothers to benefit from PMTCT interventions. In the US, oral fluid HIV testing was shown to be feasible and highly convenient in one of the busy dental practices with a large proportion of respondents indicating that they would have declined the test had it been invasive (involving a blood draw). In keeping with the highly recommended provider initiated "opt out" HIV counseling and testing approach, not only can the oral fluid testing be adopted and extended to dental practices in resource settings but also to all healthcare points where routine HIV testing practice has remained low to further facilitate timely universal HIV care access.

Continued on page 10

OraQuick shortfalls

A downside to the oral fluid rapid test is that it is an antibody test; like many other antibody tests, it gives your HIV status as of about 3 months ago and may not be very useful during the window period when sero-conversion has not taken place. It is important to note that infections during that time can be missed and yet this is one of the periods with the greatest potential risk of HIV transmission. This information is critical for end users of OraQuick, especially for those individuals considering its use as a point-of-sex test.

Many pessimists against the OraQuick test front its potential and ease of being used as a forceful test by individuals with unwilling sexual partners; a positive test result could therefore end up being catastrophic. Also, given that there is no mandatory counseling, an unexpected test result may have adverse behavioral and emotional effects, particularly in communities where HIV stigma still prevails. In light of this, OraSure, the company that manufactures the test, put the price at $40 (about SHS 100,000) to provide for a call center manned by professional counselors where individuals can call in for counseling either prior to or after using the test, facilitating linkages to care. This cost is higher than the cost of tests sold to clinics, which is at $17. The high cost for personal tests is a major impediment as many may not be able to afford repeat tests.

While this approach may be considered and adopted by other countries to curb the large numbers who are lost to follow up after an HIV initial test, many advocates are worried that this could be a hitch in the HIV "treatment as prevention" strategy. People who have access to these personalized tests may counter the availability of pre and post-test counseling as well as linkage to care with point of care testing. Despite the shortfalls, one could argue that knowing one's HIV status with the OraQuick test would imply safer sex practices since the current increase in new infections is driven by those who don't know their status. This would all depend on ease of accessibility to care once one has tested HIV positive.

Conclusion

The OraQuick HIV test is an innovation that facilitates quick, easy and accurate HIV diagnosis with a high positive predictive value in high HIV prevalence settings. Though a little costly compared to other rapid tests, with a risk of reducing avenues of linkages to chronic care, these challenges can be offset by innovations in the ever increasing and improving advances in information and mobile technologies for health. Clearly, one has to be tested before he can be linked to care. If the painless OraQuick test can facilitate this test in programmes, communities and individuals who can afford it and who otherwise would be missed out, then why not give it a try.

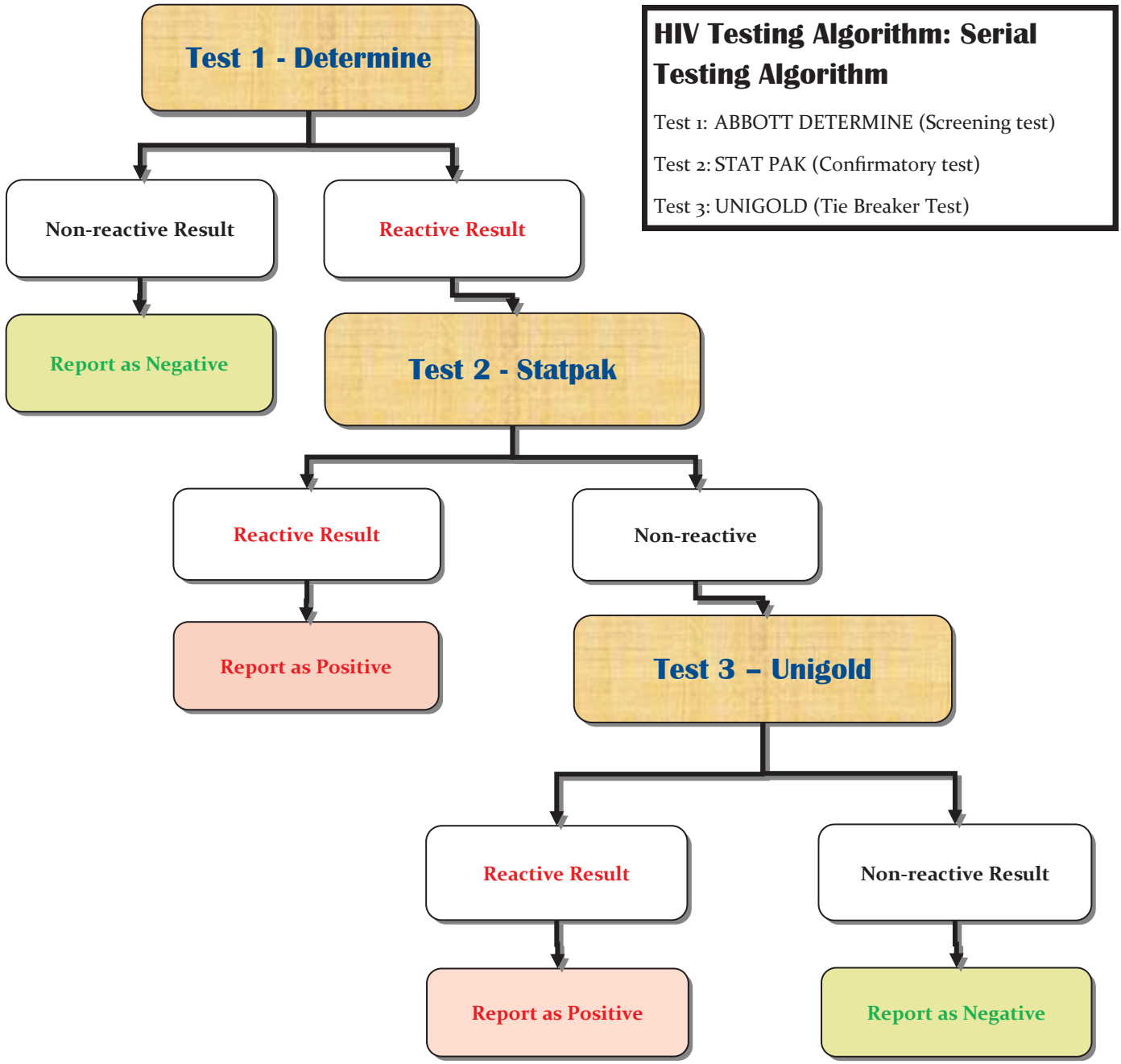
ATAZANAVIR/RITONAVIR FREQUENTLY ASKED QUESTIONS | *Continued from page 3*

Question	Facts in relation to ATV/r
TB treatment	Atazanavir, as with Lopinavir should not be coadministered with rifampicin, alternative therapeutic options should be followed.
Hepatitis co-infection/other liver disease	Safe for use in liver disease
Pregnancy	ATV/r can safely be used in pregnant and breastfeeding women.
Pediatric patients	Approved for use in children >6 years
Pill burden	ATV/r is now available as fixed drug combination (FDC). The single pill This once daily dosing single FDC pill improves adherence and is much preferred by patients
Laboratory monitoring	Liver function test (LFT's) are indicated especially when jaundice occurs to RULE OUT other causes of hyperbilirubinemia Renal function/Creatinine Clearance: consider if using with TDF but not necessary Viral load: Consider for proactive switching but not necessary
Food	Must be taken with food
Common Drug-Drug interactions	Rifampicin: Rifampicin is a cytochrome CYP 3A inducer and should not be used with ATV/r Tenofovir: ATV/r increases TDF levels while TDF slightly decreases ATV/r levels. No evidence that this has clinical significance (unless patients are on both drugs and an H2 blocker) Antacids (Proton Pump Inhibitor's and H2 blockers): Both decrease absorption of ATV/r. H2 blockers should be taken separately if used. PPIs should not be co administered with ATV
Availability	ATV/r is now readily available across ALL warehouses in Uganda (NMS, JMS and Medical Access)
What 3rd line options for treatment are available?	Also, ATV is unique among PI's in that its signature resistance mutation, I50L, confers resistance to ATV but increased susceptibility to many other PIs, including LPV/r. Use of ATV/r in 2L potentially allows for a viable 3L option using LPV/r in resource-limited settings.

ATIC Newsletter—Correction

Dear Reader,

In our last issue under the article "Rapid testing for HIV diagnosis," we erroneously ran a HIV test protocol. This is the correct rapid HIV testing algorithm as recommended by the Uganda Ministry of Health for HIV Testing.



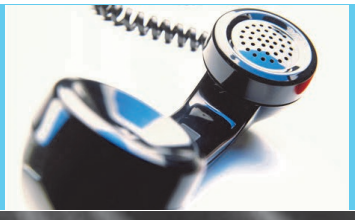
HIV Testing Algorithm: Serial Testing Algorithm

Test 1: ABBOTT DETERMINE (Screening test)

Test 2: STAT PAK (Confirmatory test)

Test 3: UNIGOLD (Tie Breaker Test)

Have a question or comment? You can always call ATIC on toll free number: **0800200055** for free advice on patient management. You can also beep or SMS ATIC on **0717326500**.



By: Dr. Christine Kihembo, ATIC Team Leader

Ask ATIC

Q: BB is a 35 year old female who has been on ART for about 5 years since 2008. About two months ago she was switched to second line ART (TDF/3TC/Atazanavir) following immunological and clinical failure on AZT/3TC/EFV. She has come in for her drug refill but she also reports yellowing of eyes which she noticed about three weeks following second line ART initiation. She reports no associated symptoms such as abdominal pain, nausea or vomiting and her stool/urine are of the usual colour. She has no associated fever and has good appetite. She has noted that the yellowing of the eyes has slowly but progressively increased over time. Other than septrin prophylaxis, she is not on any other medication/supplement and has never experienced similar symptoms in the past. BB is on once daily dosing of TDF: 3TC:ATV/r , 300mg: 300mg: 300mg/100mg respectively. Clinically she is looks well, afebrile, not anaemic but with mild-moderate scleral jaundice. The abdomen is soft, non-tender with no palpable organs. Other systems are all normal.

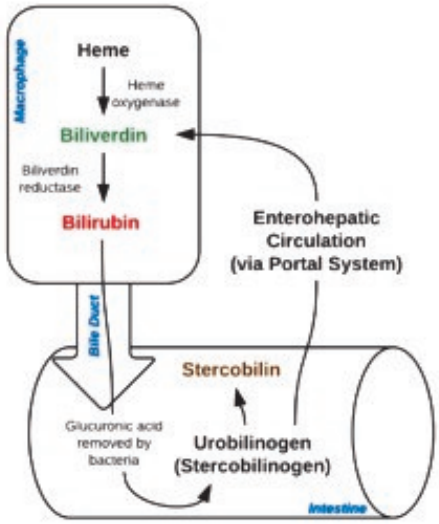
Could this be ART related and should I stop the medication?

A: Most likely BB has ATV induced hyperbilirubinaemia with jaundice which would not call for stopping ATV unless there is associated liver damage or it is of significant cosmetic concern to BB.

Increased serum bilirubin (hyperbilirubinaemia) is the most common documented side effect of Atazanavir. Bilirubin, a yellow pigment in the blood is present in blood, urine or stool and is a by-product of haemoglobin breakdown. Haemoglobin is the oxygen carrying molecule in the body.

Normally the body produces bilirubin and gets rid of it through mainly stool and to a less extent urine. When Bilirubin is formed in the reticulo-endethial system, it is bound to albumin (unconjugated bilirubin) to be transported in blood to the liver. Inside the liver cells, conjugation occurs: bilirubin is made soluble by attaching to glucuronic acid catalysed by the UDP-glucuronosyl transferase enzyme(UDPGT). The conjugated bilirubin is excreted into bile and drains into the duodenum and then gut. In the terminal ileum and colon, it is then broken down by gut normal flora to stercobilin which is excreted in faeces as shown in the diagram below.

Haemoglobin breakdown



Increased Bilirubin levels is thus usually due to increased production as occurs in haemolysis, impaired bilirubin conjugation as occurs in liver disease, impaired excretion or due to regurgitation bilirubin as occurs in from damaged or blocked bile ducts.

During its metabolism, Atazanavir competitively inhibits the UDPGT enzyme leading to accumulation of unconjugated Bilirubin. This is particularly so in patients with a genetic predisposition with specific allele variants of the UDTA. When boosted with ritonavir (ritonavir inhibits the cytochrome p450 system), higher serum levels of Atazanavir necessary for HIV viral suppression are achieved but this also increases the risk of hyperbilirubinaemia.

Elevated serum bilirubin alone or with clinical jaundice affects up more than 35% of patients starting Atazanavir with no associated liver dysfunction and is usually totally reversible once the drug is stopped. Clinical jaundice occurs when serum bilirubin exceeds 3mg/dl.

Diagnosis

BB seems to be experiencing Atazanavir induced hyperbilirubinaemia in view of: the clinical jaundice with no other apparent suggestion of hepatic injury; haemolysis; infection; Patient is clinically well and the fact that she is newly on ATV.

However this can only be confirmed by laboratory investigations; First of all, establish that it is unconjugated bilirubin predominant in this patient (normally conjugated bilirubin forms up to 30% of the total bilirubin) Secondly, confirm that there is no liver dysfunction as shown by normal Liver function tests particularly AST, ALP, and albumin and prothrombin time. Rule out other common infections such as Hepatitis A and Hepatitis B.

Conclusion

Hyperbilirubinaemia with or without jaundice is rarely an indication for stopping Atazanavir except for cosmetic reasons or in rare circumstances when the bilirubin reaches toxic levels of greater than 6mg/dl. BB can be reassured and encouraged to continue with ATV once ATV induced hyperbilirubinaemia is established with no associated derangement in liver function. However she should be evaluated and substitution to an alternative protease inhibitor considered if the jaundice will interfere with adherence or bothers her cosmetically.