THE REPUBLIC OF UGANDA
MINISTRY OF HEALTH

MAKERERE UNIVERSITY

INFECTIOUS DISEASES INSTITUTE

ATIC Newsletter, Vol 15, Issue 1,
February 2022.

HIV DRUG RESISTANCE

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Introduction

The introduction of antiretroviral drug therapy has reduced morbidity and mortality associated with (Human Immunodeficiency Virus) HIV infection and resulted into long term survival of HIV patients (1). Unfortunately, the effectiveness of these antiretroviral therapies has been reduced by the emergence of HIV drug resistance (HIVDR) (1). In simple terms, HIVDR refers to the ability of HIV to replicate in the presence of drugs that usually suppress its replication. A study showed that 76% of their study population exhibited resistance to one or more antiretroviral drugs (1). While exposure to antiretroviral drugs selects for resistant HIV strains, even drug-naive patients may be infected with strains of the virus that are resistant to drug therapy (2). The latter is referred to as primary HIVDR. The presence of antiretroviral drug resistance is an important cause of treatment failure in HIV patients and the resistance has often been documented to cut across multiple classes of antiretroviral drugs (1), significantly complicating HIV therapy. A significant population-level HIVDR could potentially restrict future therapeutic options and increase treatment costs by requiring new and more expensive antiretroviral (ARV) regimens. HIVDR could also hinder progress towards the global goal of ending the epidemic by 2030.

In Uganda, Since the early 2000s, the Ministry of Health (MoH) has progressively rolled out the public sector anti-retroviral treatment (ART) programme that provides free ART through accredited health facilities. The number of people on ART has increased from 20,000 in 2003 to over 1,000,000 by the end of 2017 (3). In 2014, the MoH adopted the WHO/UNAIDS 2020 targets and by the end of 2017, it was estimated that there were 1,324,685 people living with HIV in Uganda (3). Of these 1,189,811 (90%) knew their HIV status; of those who knew their HIV status, 1,140,420 (96%) were on treatment and of those on treatment, 992,165 (87%) had viral suppression (3). In 2016, Uganda conducted an HIVDR survey among adults initiating or reinitiating ART, yielding an overall weighted HIVDR prevalence of 18.2% (4) with the highest noted for Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs) at 14.1% (4).

Primary HIVDR is a profoundly understudied topic, in the face of poor viral suppression rates among children. Of all people living with HIV globally, 66% are virally suppressed (5). However, the rate of viral suppression differs between children and adults with lower rates among children as evidenced by data from UNICEF report 2021 i.e. In Malawi, 42% of the children are virally suppressed (adults at 67%), in Uganda children are at 49% viral suppression (adults at 84%), Zimbabwe at 47% (adults at 86%) (6).

A study done in Uganda showed 10% prevalence of primary HIV Drug resistance (HIVDR) among all children and 15.2% among children under three years (7). The high level of resistance was attributed to previous PMTCT exposure that occurred in 35.7% of prevention of mother-to-child transmission (PMTCT)–exposed children (7).

One critical driver of poor viral suppression in children is suboptimal ART regimens (8). This is secondary to lack of palatable paediatric formulations, higher cost of Protease Inhibitors (PIs), and scarcity of paediatric-trained clinicians which contributes to prolonged use of failing regimens in children (9).

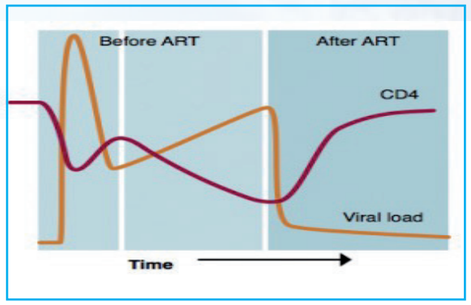
Many children living with HIV in Uganda have been faced with multiple biopsychosocial issues leading to adherence issues that stem from medicine-related challenges, care-giver challenges, and health facility challenges. These challenges lead to viral non-suppression, thus limited growth and disease progression (10).

HIV drug resistance testing is proving to be a powerful tool that can help clinicians tailor their treatment regimen to the specific HIV strain(s) that infect their patients. In addition, numerous new agents and classes of antiretroviral drugs are currently under development in an effort to keep pace with emerging HIV drug resistance. Successful treatment of HIV requires a detailed knowledge of the various mechanisms by which resistance can arise as well as an understanding of strategies for overcoming resistance once it occurs.

HIV Basic information:

HIV is a virus that attacks the body's immune system and if not treated leads to Acquired Immunodeficiency Syndrome (AIDS) (11). Without ART the natural history of HIV is shown in (fig 1) below depicting viral load and CD4. In its spread, HIV is transmitted sexually, vertically through mother to child transmission during pregnancy, delivery, breastfeeding, and through contact with infected blood or sharps (11).

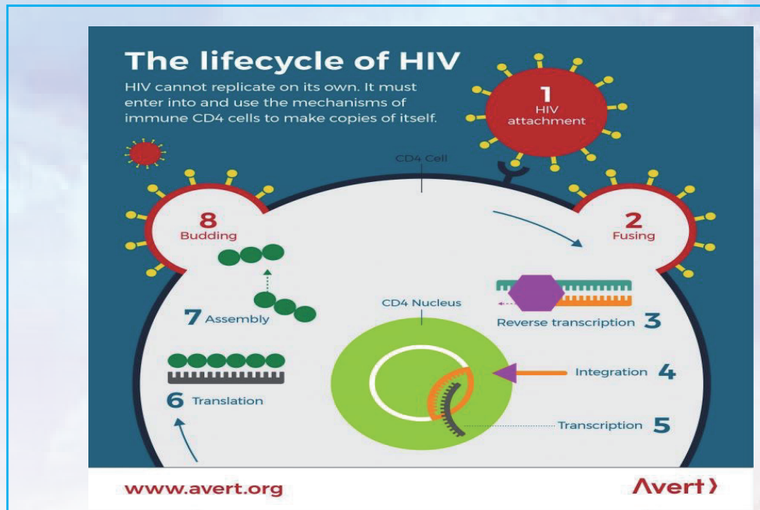
Fig 1: HIV Natural History



HIV LIFE CYCLE

The HIV life cycle is typically divided into seven distinct stages, from the attachment of the virus to the host cells to the budding of new free-circulating HIV virions (11). In this cycle, (fig 2), outlined below, it makes mistakes due to the lack of proofreading. This results into multiple variants from the original species (11). It's very important to understand these stages because this is where the ARVs target.

Fig 2: The HIV life cycle is typically divided into seven distinct stages:



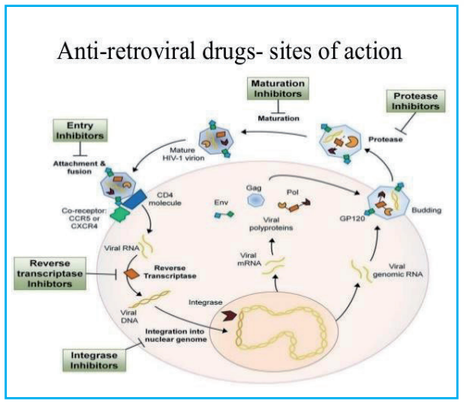
- Viral attachment:
  To infect the cell, HIV must attach itself by way of a lock-and-key system onto CD4 cells using gp120 and gp41 (11).
- Binding and fusion: Once attached to the cell, HIV injects proteins of its own into the cytoplasm of the CD4 cell. This causes fusion of the cell membrane to the outer envelope of the HIV virion via co-receptors CCR5 and CXCR4. The virus then un-coats (11).
- Reverse transcription: The single-stranded RNA of HIV must be converted to the double stranded DNA. It accomplishes this by use of enzyme reverse transcriptase. Once converted to DNA, the genetic machine has the coding needed to enable viral replication (11).
- Integration: For HIV to hijack the host cell's genetic machinery, it must integrate the newly formed DNA into the nucleus of the cell, thus integration into host DNA (11).
- Transcription and translation: Upon integration, more transcription occurs leading to formation of mRNA and translation into viral polyproteins (Env, Gag, Pol) (11).
- Assembly: HIV must manufacture protein building blocks that it uses to assemble new virus. It does so with the protease enzyme which chops protein into smaller bits and then assembles the bits into new, fully formed virions (11).
- Maturation and budding; Once the virions are assembled, they go through the final stage in which the mature virions bud off from the infected host cell. Once released into free circulation, these virions go on to infect other host cell and begin the cycle yet again (11).

ANTIRETROVIRAL THERAPY (ART)

These are drugs that have been developed to hinder HIV viral replication with the major goal of achieving viral suppression that progressively would result into immune reconstitution, reduced morbidity and mortality, good quality of life and lastly reduced HIV transmission (11). Currently, there are six classes of approved ARVs available that act at the different stages of the HIV life cycle. These include:

- CCR5 Inhibitors like Maraviroc.
- Fusion inhibitors like Enfurvirtide.
- Nucleoside reverse transcriptase inhibitors (NRTIs) like Abacavir, Tenofovir, Zidovudine, Lamivudine, Emtricitabine.
- Non-nucleoside reverse transcriptase inhibitors (NNRTIs) like Efavirenz, Nevirapine and Etravirine.
- Integrase inhibitors like Dolutegravir, Raltegravir, Elvitegravir.
- Protease inhibitors like Lopinavir, Atazanavir, Darunavir (all boosted by ritonavir).

Fig 3: ART sites of action. Copyright (12)



These antiretroviral drug therapies have dramatically reduced morbidity and mortality associated with HIV infection achieving the major goals. Unfortunately, the effectiveness of antiretroviral therapy has been markedly reduced by the emergence of HIV drug resistance. In 1987, the first ARV drug was developed (Zidovudine) (11) and later other drugs. In the early treatment of HIV Zidovudine was successful, however, HIV resistance emergence towards it complicated the situation. Research that followed showed that the use of combination drug therapies could significantly improve HIV patients' chances for long-term survival by delaying the occurrence of drug resistance.

The WHO defines two forms of HIV drug resistance (3):

1. Acquired HIVDR (ADR): This develops when HIV mutations emerge due to viral replication in individuals receiving ARV drugs.

2. Primary/Transmitted HIVDR (TDR): This is detected in ARV drug naive people with no history of ARV drug exposure. TDR occurs when previously uninfected individuals are infected with virus that has drug resistance mutations. Below are some important terms used in drug resistance.

TERMS USED IN HIV DRUG RESISTANCE

Genetic barrier to resistance: This is defined as the threshold above which resistance occurs (11). This is determined by the number of critical mutations required for drug resistance to develop, the level of pre-existing resistance, and the rate of replication of these pre-existing resistant strains. Low genetic barrier to resistance are first generation NNRTIs, while High genetic barrier to resistance are PI, integrase inhibitors and triple class regimens. This means that the virus may have one major mutation to NNRTIs and that renders it resistant, while it (virus) needs more than one mutation to render it resistant to PIs, integrase inhibitors and triple class regimens.

Archived drug resistance: Using standard resistance tests, some mutations might not appear after a period of ART, not because they are absent but are shelved. If treatment that selects for these mutations appears, they re-appear and contribute to treatment failure. Mutations that have less impact on viral fitness take longer to disappear. For example, M184V disappears very quickly.

HIV drug resistance: This is the ability of HIV to reproduce or multiply itself in the presence of antiretroviral drugs (11).

Wild-type virus: This refers to naturally occurring strains of HIV. It is more fit and responds well to ART (11).

Mutant virus: This is where the virus has developed mutations to the regimen that the patient is taking. This virus is less fit, and poorly responds to ART.

Signature mutation: This is a mutation that is typically associated with resistance to a particular drug e.g. K65R confers resistance to TDF.

Cross-resistance: This refers to resistance to drugs other than the drug that selected the mutation(s).

Acquired resistance: Occurs when a treatment-experienced person living with HIV develops drug mutations in the presence of drug pressure.

Primary resistance: This is when a treatment-naïve person is infected with a drug-resistant strain of HIV from someone with HIVDR mutations.

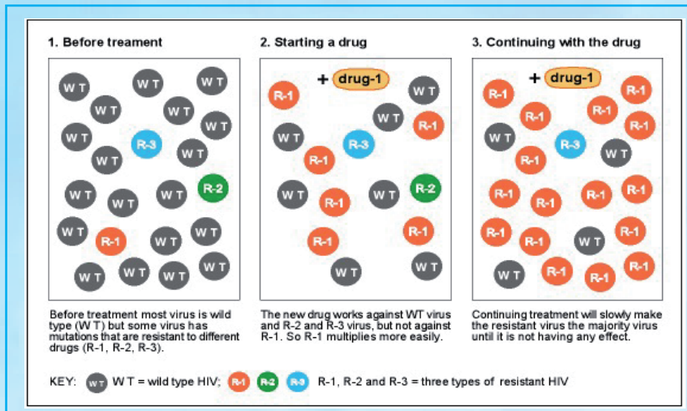
Viral blip: This refers to transient viral increase to values between 50-1000 copies which then return to undetectable without change in therapy.

Quasi species: This is a group of viruses related by a similar mutation or mutations, competing within a highly mutagenic environment.

CAUSES AND HOW HIVDR HAPPENS

HIVDR is caused by changes in the genetic structure of HIV that affects the ability of drugs to block replication of the virus. Initially, resistant mutations are caused by the rapidly multiplying error prone virus even before initiating ART (13) but after ART initiation, the selective drug pressure will cause more mutations and even more complicated resistant patterns (9).

Figure four below obtained from HIV i-base (14) demonstrates how mutations happen before treatment, at start of treatment with good adherence in presence of mutations and at holding of the medication.



It is clear from the figure above that we already have a resistant virus even before treatment. Because HIV RNA is prone to mistakes as it multiplies, there are usually many variants as an outcome. The variants are usually less fit as compared to the wild type (15) and that is why the figure before treatment is predominated by the wild type of virus. With the initiation of ART, the wild type that is sensitive to ART is wiped out leaving the resistant type, which with continued treatment multiplies and becomes dominant. Now, the ART has selected for the mutant type of virus hence it's wrong to say that ART causes resistance. With stoppage of ART, the wild type being more fit will multiply and suppress the previously selected resistant type while on treatment.

The commonest risk factor associated with drug resistance is poor adherence to ART (16,17). Others could be drug interactions, malabsorption, and primary resistance.

Adherence is the extent to which a patient follows an agreed upon prescribed treatment regimen, that is, right drug, right dose, right route and frequency. The common red flags to non-adherence are missing appointments, wrong (high or under) doses of medicine, sharing drugs, taking drugs at wrong time, drug holiday (16,18).

Measuring Adherence

There is no gold standard for measuring adherence but there are many validated tools or strategies including clinic attendance, pharmacy records, pill counts, review of treatment charts, patient/ care-giver self-report, electronic measurement devices like bottle caps/MEMS and therapeutic drug levels.

Using pill counts to determine adherence levels:

$$\%\ \text{Adherence} = \frac{\text{Number of pills taken}}{(\text{Total number of pills expected to have been taken}) \times 100\%}$$

Key to good, average and poor adherence levels, as per the daily doses in table 1.

Table 1: Determining adherence levels from self-report and pill count and recommended action

Missed doses per months		Percent adherence	Adherence ranking	Recommended Action
Oncedaily dosing	Twice daily dosing			
<2 doses	≤ 2 doses	≥95%	Good	• Review adherence plan • Support to continue adhering well.
2-4 doses	4-8 doses	85–94%	Average	• Address the causes of average/poor adherence • Review adherence plan
≥5 doses	≥9 doses	<85%	Poor	
Note: Adherence >105% could imply potential drug sharing or other inconsistencies in dosing and should be investigated.				

- Good adherence aims at viral suppression and avoiding resistance which are good indicators of excellent response to ARVs.

Common Class Resistance Mutations:

As noted earlier there are different stages during HIV viral multiplication and different classes of ARVs have been developed to inhibit viral multiplication at these different stages. The virus will develop resistance to particular ARVs by developing changes in their genetic makeup (mutations). This can happen either as a result of prolonged period of time on treatment or more commonly, as a result of suboptimal treatment adherence.

Characteristics of mutations:

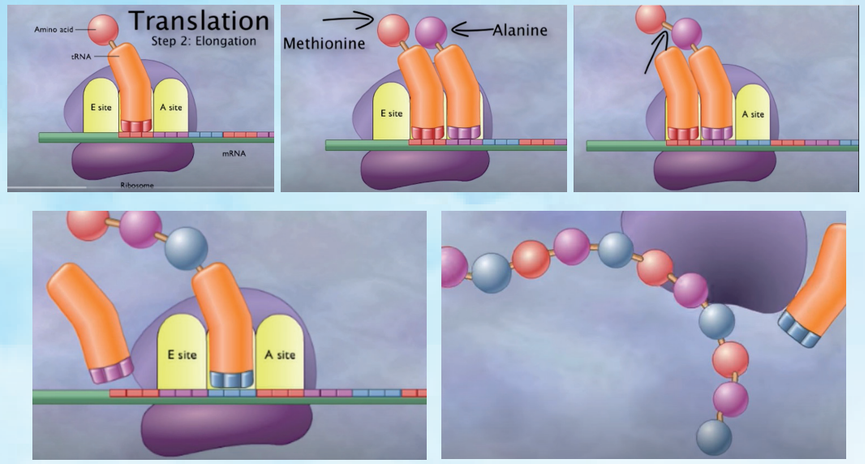
- Some mutations have clinical significance while others don't. Those with clinical significance cause resistance to ART targeted by that mutation.
- Some mutations affect only one drug, but others cause cross resistance across the whole class. For example; K103N affects Nevirapine and Efavirenz.
- Some mutations are pathognomonic of drugs, for example, K65R-resistance to Tenofovir.
- Wild type virus is more fit than mutated virus.
- Mutations can emerge within days of insufficient drug pressure.
- Mutations persist indefinitely and can re-emerge if the same drug is stopped and re-started resulting in archived mutations.
- Major mutations have a big impact on drug resistance. M184V results in high level resistance to 3TC/FTC and low level resistance to ABC but it (M184V) gives a half crippling effect on the virus increasing its susceptibility to TDF, AZT, and others.
- Minor mutations only have a small impact on drug resistance.

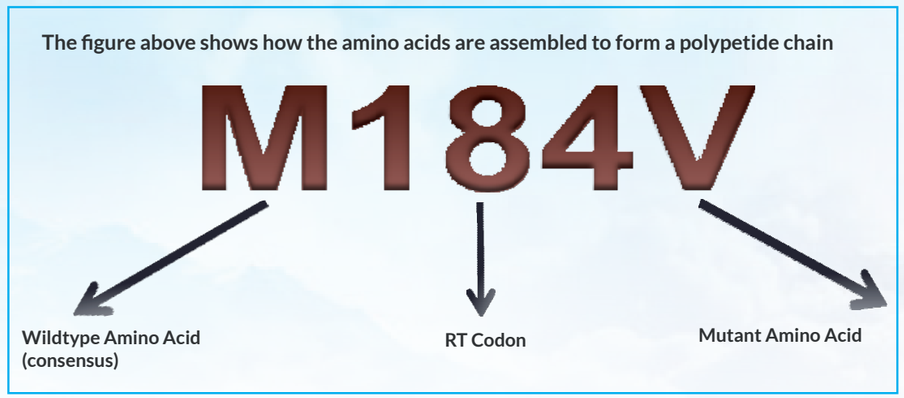
Nomenclature/Naming of mutations

Amino acids make up the substrates DNA formation

A- Alanine, C – Cysteine, D – Aspartate, E – Glutamate, F - Phenylalanine, G – Glycine, H – Histidine, I – Isoleucine, K – Lysine, L – Leucine M – Methionine, N

– Asparagine, P – Proline, Q – Glutamine, R – Arginine, S – Serine, T – Threonine, V - Valine, W – Tryptophan, Y – Tyrosine





This means, in this particular virus at position 184, the original amino acid methionine has been replaced by amino valine forming a new mutant virus.

RESISTANCE TO NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTIs)

- Usually the NRTIs work at the active site of the RT enzyme by actively competing with the naturally occurring substrates for the active site(11). The drug is picked up and added to the polypeptide chain being formed hence blocking the addition of more proteins (11). The resistance to this pathway follows two mechanisms:

Discrimination pathway: The reverse transcriptase (RT) enzyme is able to avoid binding of the NRTI, while retaining the ability to recognise the natural nucleotides. Examples of mutations using this are K65R, L74V, Q151M and M184V (11).

Primer unblocking: The enhanced phosphorolytic removal of the chain-terminating NRTI from the 3′-terminus of the primer after it has been incorporated into the viral DNA(11). This pathway is used by Thymidine Analogue Mutations (TAMs).

RESISTANCE TO NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs)

NNRTIs usually work in an allosteric way. They do not work at the active site but attach on the side of the RT enzyme called the hydrophobic pocket [5]. With this, they change the shape of the active site where the natural substrates can no longer fit or attach. In resistance to these NNRTIs the virus makes changes in the hydrophobic pocket where the NNRTIs can no longer attach (11).

Resistance to Protease Inhibitors (PIs)

PIs bind specifically to the active site of the enzyme thereby preventing the HIV-1 protease from cleaving the two Gag and Gag-Pol precursor proteins, which results in the formation of immature non-infectious virus particles (11).

The development of PI resistance is believed to be a stepwise process(11). These first resistance mutations to develop are also referred to as **primary mutations** (11). They are located near the substrate binding of the enzyme resulting in conformational changes. By changing the structure of the substrate-binding cleft, these primary mutations interfere with the binding of the PI to the viral protease, resulting in resistance to PIs (11).

The altered structure of the substrate-binding cleft has a knock-on effect and the viral protease is less able to cleave its natural substrate, resulting in a reduced replicative capacity of the virus (11). Thus, the development of PI resistance comes with a fitness cost for the virus. During continuous PI therapy, additional mutations emerge in the protease, which are commonly referred to as secondary or accessory mutations. Secondary mutations may also be compensatory, restoring protease enzyme activity and/or enhance the resistance of primary mutations.

Resistance to Integrase

This inhibits the integrase enzyme from performing strand transfer by binding to the active site of integrase (11).

Changes are at the active site of the integrase enzyme, where the drugs can no longer attach.

MONITORING ART RESPONSE AND TESTING FOR RESISTANCE

Monitoring of response to ART can be done through **Viral load monitoring** (19). Viral load monitoring is done starting at six months after initiation of ART, at 12 months on ART and thereafter, annually for adults who are virally suppressed (19). For children, adolescents, pregnant and lactating mothers, however, the viral load testing is conducted every six months (19).

When a viral load is >1000 copies/ml, intensive adherence counselling (IAC) is done for at least three months (19) to assist the client to overcome their specific barriers to adherence, then viral load testing is repeated. HIVDR is suspected when 2 consecutive viral loads are >1000 copies/ml despite IAC (19). Detection of drug resistant Virus can be done for patients that are suspected to be failing on treatment so as to determine the next best regimen.

The rationale for the threshold of 1000 copies/ml was based on two main sources of evidence. First, viral blips or intermittent low-level viremia

(50–1000 copies/ml) can occur during effective treatment but have not been associated with an increased risk of treatment failure unless low-level viremia is sustained (20). Second, clinical and epidemiological studies show that the risk of HIV transmission and disease progression is very low when the viral load is lower than 1000 copies/ml(20).

Laboratory Eligibility Criteria for Testing ART Drug Resistance

HIVDR is not performed for all patients with a detectable viral load in Uganda. For patients to be eligible for HIVDR testing, they should have been adherent to their ART for at least one month before the sample is taken off, and have: 1. A confirmed detectable VL from two independent consecutive samples collected after an undetectable measurement, or 2. A steady or increasing VL after the initiation of medications (HIV RNA levels >1000 copies/mL), or 3. A detectable VL six months after treatment initiation (20).

Laboratory Eligibility Criteria for Testing Drug Resistance in PLHIV in Uganda

All children below 15 years failing on first line(20). This allows for all children below 15 years in two categories;

1. Children on NNRTIs based regimens with a non-suppressed viral load.
2. Children on LPV/r or DTG based regimens with a non-suppressed repeat viral load following two consecutive good IAC sessions.

Adults would be considered when they are on second line regimen, and they have non-suppressed repeat viral load results following three consecutive IAC sessions

Choice of sample

While plasma is the preferred sample for HIVDR genotyping, plasma analysis requires sophisticated laboratory equipment, personnel, space, and stringent storage conditions for maintenance of sample integrity and transport. The field has gained substantial experience with the dried blood spot (DBS) technique as an alternative. All laboratory staff must be properly trained and deemed competent to perform their duties.

Sample collection

Proper sample collection is a very vital part of laboratory investigations. Whole venous blood should be collected in EDTA tubes to obtain plasma while DBS samples should be collected using finger prick to obtain capillary blood.

Transportation

Plasma or whole blood should be transported at room temperature to the laboratory on the same day. Clinic staff should ensure that DBS samples dry completely then, transport them in Ziploc bags with a desiccant and humidity indicator at room temperature.

Storage

Laboratory staff should store plasma and whole blood at -80c if the samples won't be tested immediately. However, DBS samples can be store at -20c until they are tested.

Interpretation of results

Drug-resistant mutations may be related to transmission of a drug-resistant virus at the time of initial infection or may arise due to continued virus replication in the presence of drug due to poor drug adherence. In treatment-experienced patients with virologic failure, it is preferable to obtain resistance testing while the patient is taking antiretroviral therapy (ART) or is within weeks of discontinuing treatment. However, this might not be possible in patients who are non-adherent to their regimen. In the absence of drug pressure, the wild-type HIV strain may become dominant. Although some mutations may persist off ART, the results can be misleading if drug resistance testing is performed when patients are not receiving ART.

Similarly, resistance testing is less reliable at detecting resistance to classes of drugs no longer being taken. These limitations emphasize the importance of taking a complete medication history.

WAY FORWARD FOR CHILDREN

To achieve viral suppression, ART programmes require targeted efforts to provide specific health facility requirements, psychological and economic needs of patients and ART-treated children and their caregivers. Integration of HIV treatment with programs for orphans and vulnerable children may improve viral suppression rates (21).

Other facilitators of adherence that were reported from a study by Fetzer, B et al in DR Congo include the child's knowledge and understanding of HIV, assistance or increased psychosocial support from a vigilant caregiver or other family member, having a routine or strategy to maintain good adherence like keeping medicine in the same spot, setting alarms to remind about time for taking medicine, and motivators for children including gifts but some used fear of the effects of missed doses (22).

Recommendations from multiple reports, including a recent study on drug resistance mutations among South African children living with HIV (23) are:

- Use of PI based ART regimens as first line for all young children.
- Overcome logistic barriers to always avail palatable paediatric regimens.
- Always super boost PIs or provide alternative regimens for children with HIV/TB co-infection.
- When appropriate, use Dolutegravir (DTG) based regimen like for children >20Kg or when dispersible DTG is available.
- Second line regimens should be AZT or TDF based because the M184V mutation causes hyper-susceptibility of HIV to AZT and TDF not ABC [Diallo K, Gotte M. Molecular impact of the M184V mutation in HIV type 1 reverse transcriptase].
- More studies to estimate the extent of primary HIVDR in paediatric patients in order to inform current treatment guidelines.

THIRD LINE REGIMENS

When a patient has treatment failure on second line regimens, and a drug susceptibility test is done, a switch meeting is usually convened to discuss the possible 3rd line regimen. This depends on the level of resistance detected to the different drugs, but also the drug-interactions, pill burden, side effects and psychosocial issues. The common third line available drugs in Uganda are Dolutegravir, Raltegravir, Darunavir, Ritonavir, Etravirine, TAF/3TC (19).

Third line regimens available for children include drugs like:

(i) TDF/3TC/DTG for those who did not get DTG in their first or second line regimens.

(ii) Raltegravir.

(iii) Darunavir/ ritonavir.

(iv) Etravirine and TAF/ 3TC.

Specific dosages can be obtained from the available ART job aids.

Reporting and Ordering for Third Line ART Medicines:

Supplies for third line ARV medicines have been streamed as follows;

- Public health facilities and PNFP health facilities with patients on third line outside Kampala and Wakiso will receive their Third line ARV medicines through the Regional Referral Hospitals in their region which get their supply from NMS.

- Centres of Excellence (JCRC, Baylor Mulago, TASO Mulago, IDI Mulago, Mildmay Uganda, TASO Entebbe) receive their Third line ART supplies from the attached Regional Referral Hospital as follows; Kiruddu NRH= JCRC, TASO Entebbe and Mildmay Uganda. China-Uganda Friendship Hospital Naguru= Baylor, IDI and TASO Mulago.

- PNFP health facilities in Kampala and Wakiso with patients on Third line will receive third line ARVs through the nearby COEs.

- Public health facilities with patients on Third line in Kampala and Wakiso will receive their third line ARVs through China-Uganda Friendship Hospital Naguru.

Reporting HIV DR; Dashboard, Access, and Authorization

Implementation of the dashboard was conceptualized as follows:

1. New viral load results entered in the VL LIMS system at CPHL are funnelled through the HIVDR testing eligibility algorithm and eligible sample profiles are then pushed to the HIVDR database in real-time.
2. On the database, an eligible sample profile is referred to the HIVDR lab along with the corresponding physical sample and the facility is notified via an automated email about the referral and requested to fill the patient's medical and social profiles within the database itself ahead of the Switch Committee sitting.
3. Once the HIVDR lab has tested the sample, the HIVDR result is pushed to the HIVDR database by matching it to the sample profile captured in step 1 using unique patient IDs.
4. The Switch Committee can now access the HIVDR result along with the medical and social profile of the patient and make a switch decision, all in the same database. The facility will also be able to see the decision, and to report when the patient is started on the assigned regimen in the same database.

The patient is placed under a six-month cohort and the facility will be able to access an auto-generated list of all patients due for the routine assessment in the database in real time.

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ASK ATIC

Question: Dear ATIC, what is the current guidance on DTG dosing in relation to weight among children?

Answer: According to the 2020 MOH guidelines, DTG can be used for children of all weight categories. MoH has procured DTG 10mg for use in children below 20kg.

Question: Dear doctor, I have a client on ART who has been on fluconazole for two years. Serum CrAg today was positive but client has no symptoms and signs of meningitis.

Answer: A follow-up in France of patients on ART and cryptococcal disease showed that 29% patients had positive serum CrAg at 48 months. Clinicians should discontinue fluconazole basing on the criteria below irrespective of the serum CrAg result.

Criteria to stop after a minimum of 18 months of maintenance phase:
Adults: VL<1,000 copies/mm^3 & CD4 ≥ 200 or CD4 ≥200 (if viral load not available) after 12 and 18 months
Children: If CD4>25% or viral suppressed

Question: Dear Doctor, I have a 26 kg adolescent on LPV/r with a non-suppressed viral load. He suggests changing his dosing to one in the morning and two in the evening to increase his adherence to the medication, is this something I can do?

Answer: No, you may not make such dose adjustment because this will be inappropriate dosing for the age, which may pose a risk of drug resistance.

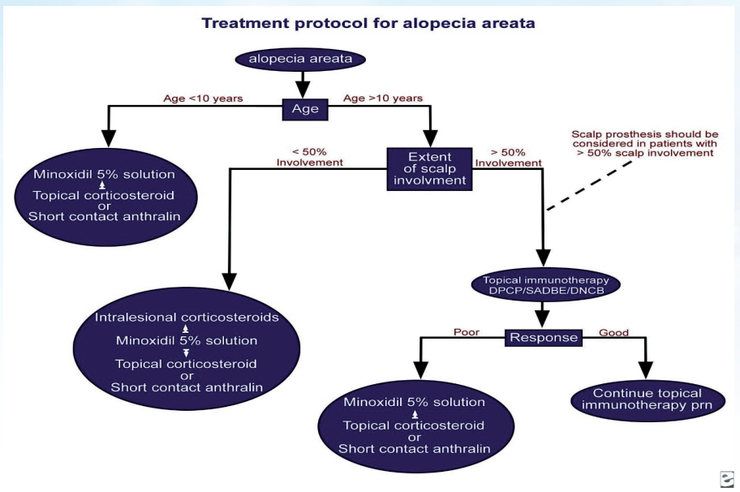
Question: I am a midwife in a HC 3, how do I prevent neonatal hepatitis B infections in babies born to Hepatitis B positive mothers?

Answer: WHO recommends an immunoglobulin and hepatitis B vaccine be given to the baby within 72 hours of delivery. Subsequent Hepatitis B vaccines are given at six weeks and six months.

Question: Hello ATIC, can I vaccinate a person ON cART and non-suppressed viral load for COVID19?

Answer: Yes, People living with HIV at any CD4 cell count appear to be at increased risk for severe outcomes and death due to COVID-19 compared with people without HIV. The currently available vaccine products are not live vaccines; they include genetic material from SARS-CoV-2 which cannot replicate. Therefore, these vaccines are not expected to be less safe in people who are immunocompromised.

Question: Hello Doctor, I have a middle aged woman with a 1-month history of progressive hair loss (see attached image). How best can I manage the client?



Reference

1. Zdanowicz MM. The pharmacology of HIV drug resistance. Am J Pharm Educ. 2006 Oct 15;70(5):100.
2. Weinstock HS, Zaidi I, Heneine W, Bennett D, Garcia-Lerma JG, Douglas JM, et al. The epidemiology of antiretroviral drug resistance among drug-naive HIV-1-infected persons in 10 US cities. J Infect Dis. 2004 Jun 15;189(12):2174–80.
3. National HIV Drug Resistance Prevention, Monitoring and Surveillance Activities, National Status Report [Internet]. 2018. Available from: https://www.uvri.go.ug/sites/default/files/files/HIVDR%20REPORT%20%20_Draft%209.pdf
4. Watera C, Ssemwanga D, Namayanja G, Asio J, Lutalo T, Namale A, et al. HIV drug resistance among adults initiating antiretroviral therapy in Uganda. Journal of Antimicrobial Chemotherapy. 2021 Sep 1;76(9):2407–14.
5. Global HIV & AIDS statistics — Fact sheet [Internet]. [cited 2022 Jan 6]. Available from: https://www.unaids.org/en/resources/fact-sheet
6. Understanding and Improving Viral Load Suppression in Children with HIV in Eastern and Southern Africa. UNICEF; 2021.
7. Kityo C, Boerma RS, Sigaloff KCE, Kaudha E, Calis JCJ, Musiime V, et al. Pretreatment HIV drug resistance results in virological failure and accumulation of additional resistance mutations in Ugandan children. J Antimicrob Chemother. 2017 Sep 1;72(9):2587–95.
8. Boerma RS, Boender TS, Bussink AP, Calis JCJ, Bertagnolio S, Rinke de Wit TF, et al. Suboptimal Viral Suppression Rates Among HIV-Infected Children in Low- and Middle-Income Countries: A Meta-analysis. Clin Infect Dis. 2016 Dec 15;63(12):1645–54.
9. World Health Organization, Fund G, Prevention UC for DC and. HIV drug resistance report 2017 [Internet]. World Health Organization; 2017 [cited 2022 Jan 6]. 82 p. Available from: https://apps.who.int/iris/handle/10665/255896
10. Nasuuna E, Kigozi J, Muwanguzi PA, Babirye J, Kiwala L, Muganzi A, et al. Challenges faced by caregivers of virally non-suppressed children on the intensive adherence counselling program in Uganda: a qualitative study. BMC Health Services Research. 2019 Mar 7;19(1):150.
11. Hoffmann C, Rockstroh JK. HIV 2015/2016 [Internet]. 2015 [cited 2022 Jan 6]. Available from: https://hivbook.com/
12. Smith RL, de Boer R, Brul S, Budovskaya Y, van Spek H. Premature and accelerated aging: HIV or HAART? Front Genet. 2012;3:328.
13. World Health Organization. HIV drug resistance strategy [Internet]. 2021 update. Geneva: World Health Organization; 2021 [cited 2022 Jan 6]. Available from: https://apps.who.int/iris/handle/10665/343175
14. Resistance 3: Mutations with and without drugs | Training manual | HIV i-Base [Internet]. [cited 2022 Jan 6]. Available from: https://i-base.info/ttfa/hiv-and-drug-resistance/resistance-3-resistance-3-mutations-with-and-without-drugs/
15. De Luca A. The impact of resistance on viral fitness and its clinical implications. In: Geretti AM, editor. Antiretroviral Resistance in Clinical Practice [Internet]. London: Mediscript; 2006 [cited 2022 Jan 6]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK2244/
16. Schaecher KL. The importance of treatment adherence in HIV. Am J Manag Care. 2013 Sep;19(12 Suppl):s231-237.
17. Sebunya R, Musiime V, Kitaka SB, Ndeezi G. Incidence and risk factors for first line anti retroviral treatment failure among Ugandan children attending an urban HIV clinic. AIDS Res Ther. 2013 Nov 11;10(1):25.
18. Shumba C, Atuhaire L, Imakit R, Atukunda R, Memiah P. Missed Doses and Missed Appointments: Adherence to ART among Adult Patients in Uganda. ISRN AIDS. 2013;2013:270914.
19. MINISTRY OF HEALTH. CONSOLIDATED GUIDELINES FOR THE PREVENTION AND TREATMENT OF HIV AND AIDS IN UGANDA. 2020.
20. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach [Internet]. World Health Organization; 2016 [cited 2022 Jan 6]. 429 p. Available from: https://apps.who.int/iris/handle/10665/208825
21. Osafo J, Knizek BL, Mugisha J, Kinyanda E. The experiences of caregivers of children living with HIV and AIDS in Uganda: a qualitative study. Global Health. 2017 Sep 12;13(1):72.
22. Fetzer BC, Mupenda B, Lusiama J, Kitetele F, Golin C, Behets F. Barriers to and facilitators of adherence to pediatric antiretroviral therapy in a sub-Saharan setting: insights from a qualitative study. AIDS Patient Care STDS. 2011 Oct;25(10):611–21.
23. Hackett S, Teasdale CA, Pals S, Muttiti A, Mogashoa M, Chang J, et al. Drug Resistance Mutations Among South African Children Living With HIV on WHO-recommended ART Regimens. Clinical Infectious Diseases. 2021 Oct 1;73(7):e2217–25.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