Patient presentation

This patient is a 15 year old girl, who is presumed to have been perinatally infected with HIV. She is classified as WHO stage III, and is aware of her status. She is a maternal orphan, her mother having passed away 4 years previously. She is currently in the care of an aunt who receives her Care Dependency Grant (CDG) on her behalf. They live in a hostel, with inadequate access to good nutrition and her personal safety is at risk.

Acknowledgement

This case study was kindly provided by Dr Claire Egbers from the Wits Paeds HIV Clinics.

History

Age 13 years
At age 13, she was diagnosed with pulmonary tuberculosis (PTB) and was treated at the South African National Tuberculosis Association (SANTA) for 6 months.

After this she was in the care of her grandmother who received her CDG on her behalf. However, her grandmother used the grant for purchasing a television and building a house in KZN (a different province to where they are living) – which left insufficient funds for the patient to afford the transport.
costs needed to get her to the clinic for regular check ups.

**Age 13 years and 6 months**
Over the next 8 months she returned infrequently to the clinic. Each time she attended she was noted to be thinner and sicker. She presented with progressive weight loss, a chronic cough, recurrent lower respiratory tract infections (LRTIs), recurrent severe dermatoses, refractory chronic suppurative otitis media (CSOM) and sexually transmitted infections (STIs) with a history of rape.

During this time **TB treatment** was started empirically on two separate occasions but the patient defaulted on treatment within a month on both occasions. Each time she did this her health deteriorated further, evidenced by recurrent ear and lower respiratory tract infections and weight loss.

**Age 14 years**
On returning to the clinic she was wasted, suffering from bilateral haemorrhagic and suppurative otitis media (OM) and severe oral Candidiasis. She was started on **TB treatment** again and this time was given regular adherence counseling. Based on the improvement in her clinical condition she appeared to be adherent during this clinical phase.

**Age 14 years and 2 months**
At this time she was started on highly active antiretroviral treatment (HAART). She was put on a regimen of 3TC, **d4T** and efavirenz.

**Age 14 years and 3 months**
After 1 month of HAART she was admitted to the surgical ward with mastoiditis which was successfully treated. She continued to take her antiretrovirals (ARVs) and her health continued to improve.

**Age 14 years and 6 months**
Within 3 months she had gained weight, her CD4 count continued to climb and she had become virally suppressed (see Investigations for full results). It was noted that during this time she attended the clinic alone on almost all visits.

**Age 15 years**
She has now been on HAART for 9 months, with excellent clinical improvement.

**Differential Diagnosis**

Ongoing problems with adherence have resulted in resistance developing to the ARVs she is currently taking.

Poor nutrition coupled with inadequate **antiretroviral therapy** has resulted in a compromised immune system resulting in opportunistic infections.
Examination

Age 13 years
Weight loss
Chronic cough
Poor health

Age 13 years and 6 months
Weight loss
Chronic cough
Deteriorating health

Age 14 years
Wasted
Bilateral haemorrhagic and suppurative otitis media
Severe oral candidiasis
STI

Age 14 years and 2 months
HIV status classified as [WHO stage III]

Age 14 years and 3 months
Mastoiditis- admitted to surgical wards

Age 14 years and 6 months
Rapid increase in weight and overall health

Age 15 years
Overall excellent clinical improvement.

Age 15 years and 8 months
Weight loss and overall deterioration in health.
Lower respiratory tract infection – admitted to medical ward

Age 15 years and 9 months
Restarted on HAART

Age 16 years
Overall health appears to be improving. She has gained weight.

Age 16 years and 3 months
Her health has deteriorated although no weight loss has occurred.
## Investigations

<table>
<thead>
<tr>
<th>Age</th>
<th>CD4 Count</th>
<th>Viral Load</th>
<th>Weight</th>
<th>Height</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>13yrs 6mths</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Induced sputa is blood stained. TB treatment started empirically.</td>
</tr>
<tr>
<td>14yrs 2mths</td>
<td>13 (13%)</td>
<td>316 000</td>
<td>32kg below 3rd centile, 64% expected weight for age (EWFA)</td>
<td>143cm (below the 10th centile)</td>
<td></td>
</tr>
<tr>
<td>14yrs 6mths</td>
<td>280 (13.9%)</td>
<td>&lt;25 copies. She is now virally suppressed.</td>
<td>44kg. She has gained 12kg in 6 months and is now below the 25th centile.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15yrs</td>
<td>No results at this time, but she appears clinically well*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15yrs 8mths</td>
<td>8 (0.54%)</td>
<td>This is below her baseline count.</td>
<td>39kg. She has lost 5kg. She is now back down to the 10th centile.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15yrs 9mths</td>
<td>8 (0.54%)</td>
<td>No change since admittance 1 month previously.</td>
<td>43kg. She has gained 4kg while in hospital and is now below the 25th centile.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16yrs</td>
<td>83 (5.4%)</td>
<td>&lt;25 copies. Once again she is virally suppressed.</td>
<td>45kg. She is still below the 25th centile</td>
<td></td>
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</tbody>
</table>
### Table

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<td>16yrs 3mths</td>
<td></td>
<td>1 200**</td>
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</tbody>
</table>

*She defaults on her treatment at this time, later reporting that she stopped taking all ARV’s at the same time.

**At this time she is only taking 3TC and EFV, she has stopped taking d4T.

### Discussion

#### Treatment and management

**Age 15 years and 8 months**

After 8 months of no ARVs she returns to the clinic, alone, she is thin and sick. She is referred to the wards and is admitted for a LRTI. Her CD4 count has decreased and her viral load has increased (see investigations for more information).

Her grandmother moved to KZN during this time, and visits her granddaughter infrequently. Our patient has been left in the care of a young aunt, age 20, who receives part of our patient’s CDG on her behalf, and the remainder is taken by her grandmother. Her reasons for stopping her ARV’s and clinic visits were financial, due to insufficient funds to afford the transport fees to the clinic and pharmacy. On questioning she claims to have stopped taking all her medication at the same time.

**Age 15 years and 9 months**
She is restarted on 3TC, d4T and efavirenz (EFV). She demonstrates her medicines well and appears to understand the importance of adherence.

**Age 16 years**
She is again virally suppressed and her CD4 count has begun to increase. She has also made a healthy weight gain (see investigations for more information).

**Age 16 years and 3 months**
Again she has problems with adherence, this time she stops only one of the drugs, d4T. She continues to take 3TC and EFV but her viral load has again increased (see investigations for more information).

**Final outcome**
At this point in her treatment it is important to address the following:
We need to establish why she has stopped part of her treatment and address this problem.

- Lack of availability of d4T at her treatment site
- Possible side effects
- Financial reasons
- Stigma

Getting her back onto triple therapy

Ideally resistance testing should be carried out for her current regimen. If resistance testing is unavailable she should be put back onto triple therapy, i.e. d4T, 3TC and EFV and her viral load monitored. Considering her previous history of rapid viral load suppression on this regimen she may have developed a 3TC M184V mutation and thus a resulting d4T hypersusceptibility. Thereby allowing greater viral inhibition by d4T. Getting d4T added back into her regimen may be sufficient to drop her viral load again.

If she does not improve on this regimen then we need to consider an entirely new regimen which would include a protease inhibitor.

She also needs to have additional cover with Trimethoprim/Sulphamethoxazole while her CD4 count is below 200, to prevent further opportunistic infections (OIs) occurring.

Her nutritional status needs to be evaluated and if necessary a dietician should be brought in to discuss her dietary options with her and help her make the best food choices available to her.

Once again issues of non-adherence need to be discussed.

If abuse of a grant is suspected social workers can refer to the guidelines published in the government gazette to act on behalf of the patient.
Evaluation - Questions & answers

**What is drug resistance?**

Drug resistance is when the virus is able to replicate in the presence of the drug and higher dosages of the drug are required to inhibit viral replication.

**What makes the virus become drug resistant?**

A change in the structure of viral proteins that the drugs target makes the virus able to replicate in the presence of the drug.

**How does drug resistance develop?**

After infection with the virus, each round of replication introduces random changes in the nucleotide sequence of the virus genome. This happens when errors are made during the copying process of viral RNA into DNA (reverse transcription) shortly after the virus penetrates a human cell. Some of the errors are made in the coding sequences of the proteins that the drugs target (such as reverse transcriptase, protease, integrase and envelope gp120/gp41). A change in nucleotide sequence alters the genetic code that specifies which amino acid will be used in the protein. Proteins with different amino acids in specific positions can prevent a drug from inhibiting the normal function of the protein. Deletions or insertions of amino acids into the coding sequence of proteins can also confer drug resistance.

**How do the changes in the structure of viral proteins make them drug resistant?**

Some of the changes affect the way the drug binds to the protein by making the drug bind more weakly (lower affinity). This means the drug will become unbound for a certain length of time and allow the protein to continue its normal function. This is a common mechanism for resistance to the inhibitors of protease (PI), integrase and the non-nucleoside inhibitors of reverse transcriptase (NNRTI). For the nucleoside inhibitors of reverse transcriptase (NRTI) there are different mechanisms such as discrimination between the inhibitor and the natural nucleotide or alternatively the removal of the inhibitor after incorporation (excision).

**What is resistance testing?**

This is testing used to see if a patient has developed resistance to an ARV. There are two types of testing: phenotypic and genotypic testing.

**Phenotypic testing:**

A sample of HIV is grown in the laboratory. A dose of one ARV is added. The growth rate of the HIV is compared to the rate of the wild type virus. If the sample grows more then normal it is resistant to the medication. This is reported as “fold” resistance. e.g. the test sample grows twenty times more then normal it has 20 fold resistance.
This is the more expensive method and takes the longest to get results.

Genotypic testing:
The genetic code of the sample virus is compared to the wild type. The code is a long chain of molecules called nucleotides. Each group of three nucleotides, a codon, defines a particular amino acid used to build a new virus. Mutations are described by a combination of letters and numbers, for example M184V. The first letter (M) is the code for the amino acid in the wild type virus, the number (184) identifies the position of the codon and the second letter (V) is the code for the altered amino acid in the mutant sample.

However resistance testing is not readily available and it is expensive. It is also not good at detecting minority mutations that make up less than 20% of the virus population. It is also only effective if the patient has a viral load over 1000 copies.

Recent research suggests that a genotypic resistance test should be done for every patient before they start taking ARVs as in the long term this is cost effective by avoiding using an ARV that won’t work.

What is the principle behind triple therapy?

Three drugs put more pressure on the ability of the virus to replicate compared to one or two drug regimens. It is due to the replication of the virus that drug resistant viruses emerge by random mutations introduced into the genome by reverse transcriptase. Limiting viral replication at a maximum level reduces the probability that a random mutation that confers drug resistance can be introduced during reverse transcription. It is also known that drug resistance mutations reduces the ability of the virus to reproduce at the same rate as the drug sensitive or wild type virus can. For this reason it is unlikely that single viruses will accumulate resistance mutations to all three drugs since these viruses would be unable to replicate efficiently. When drug resistance does emerge it is usually to only one drug and therefore these viruses will remain susceptible to the other two drugs in the regimen.

What are the risks of changing to dual therapy?

Reducing a triple regimen to two drugs lowers the level of suppression of virus replication resulting in a detectable viral load and a lower threshold for developing resistance to one or both of the remaining drugs. The third drug suppresses viruses that may develop resistance to the other two drugs. Inadequate therapy not only increases the risk of developing drug resistance due to ongoing replication of the virus, but will also increase the rate of CD4+ T cell loss and hence immune competence as well as increase the risk of virus transmission, possibly with a drug resistant strain, due to a higher viral load.

What is the benefit of this particular regimen (d4T, 3TC and EFV)?

The use of two NRTI drugs and one NNRTI drug is cheaper than using protease inhibitors or other drugs. In the absence of drug toxicity, the regimen is highly effective at reducing viral load to below detectable levels by suppression of viral replication which also minimizes the probability of resistance
developing to any of the drugs. Additionally, the drug resistance mutations that can emerge often antagonise each other and thus reduce the positive selection drug resistant viruses. This is true for the M184V mutations in reverse transcriptase that confers high level resistance to 3TC, however these viruses are highly susceptible to d4T (this is called a hypersusceptibility mutation).

**If this regimen fails, what new regimen should be considered?**

Without a drug resistance test it is not possible to predict if any drug resistance mutations that have emerged will also affect a new drug regimen. It is possible that 3TC resistance such as M184V has developed in this patient due to the removal of d4T earlier, however if adding it back in has not controlled virus replication it may be due to efavirenz resistance, possibly K103N. Although AZT and d4T have similar resistance profiles it may be an option to replace d4T with AZT. AZT suppresses 3TC resistant viruses carrying M184V and K675R mutations as well as the Y181C mutation that can confer resistance to efavirenz. If cost is not a major factor it may be worth switching to an entirely new regimen such as AZT, ddl and Kaletra.