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CASE REPORT

The First Experience of Effective 3rd Line Antiretroviral Therapy – A Case of 40-Year-Old Female Retroviral-Infected Patient at Hawassa University Comprehensive Specialized Hospital, Hawassa, Sidama, Ethiopia

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Background: Treatment failure continues to be an impediment to the efficacy of highly active antiretroviral therapy (HART) in the treatment of human immunodeficiency virus type 1 infection (HIV-1). The World Health Organization (WHO) recommends third-line antiretroviral therapy (ART) for patients who have failed second-line ART. Darunavir (DRV) boosted with ritonavir (DRV/r) has a higher genetic barrier to resistance, is active against multidrug-resistant HIV isolates, retaining virological activity even when multiple protease mutations are present, and has been shown to be cost-effective when compared to other boosted protease inhibitors (PIs).

Case Summary: This is a case of a 40-year-old female known HIV/AIDS patient who has been on ART for the last 14 years with good adherence and regular follow-up, and who is now on 3rd line ART medication with TLD (tenofovir/lamivudine/dolutegravir)+DRV/r (in her 11th month) after being diagnosed with second-line treatment failure. After 6 months and 1 week of therapy, the viral load (VL) was sent, and the result was undetectable. The patient's clinical conditions had greatly improved.

Conclusion: Third-line ART therapy, which was once thought to be a salvageable treatment, is now the primary option for second-line ART failure. TLD in combination with ritonavir-boosted darunavir is found to be effective at lowering viral loads in the blood below detectable limits. Despite a lack of data on the use of third-line ART in Ethiopia, access to third-line ART containing ritonavir-boosted darunavir is recommended because it has been shown to be an effective alternative for patients who have failed second-line ART. We recommend that more research be done with a larger sample size, and that the findings in this paper be used with caution.

Keywords: third line ART, darunavir, undetectable viral load

Introduction

The efficacy of highly active antiretroviral therapy in the treatment of human immunodeficiency virus type 1 (HIV-1) remains hampered by treatment failure.[1–3]

National programs should adopt strategies for third-line ART, which should include novel medications with low risk of cross-resistance to previously used regimens, such as integrase strand transferase inhibitors (INSTIs) and PIs, according to the World Health Organization (WHO). Clinical progression and immunological deterioration

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have been associated with treatment with newer third-line medicines. DRV/r has a higher genetic barrier to resistance than early-generation PIs, is active against multidrug-resistant HIV isolates, and has been shown to be cost-effective when compared to other boosted PIs.[4–6]

There has been limited investigation into treating people who have developed PI resistance but are expected to be vulnerable to newer drugs in the class (eg, boosted darunavir). INSTI-naive patients who were failing a boosted lopinavir regimen were tested for drug resistance, and 41% of them exhibited boosted lopinavir resistance but anticipated vulnerability to boosted darunavir, according to one study. Ninety percent of these patients achieved virologic suppression to 200 copies/mL after switching to boosted darunavir with raltegravir and either of the best available Nucleoside Reverse Transcriptase Inhibitors (NRTIs).[7–9]

Patients receiving darunavir/ritonavir had higher viral load reductions and CD4 lymphocyte increases after 24 weeks of therapy when compared to an investigator-selected Protease Inhibitor (PI), both with optimized background therapy, according to two randomized studies in treatment-experienced patients.[10–12]

In a separate trial comparing the two medications in lopinavir-naive, treatment-experienced individuals, darunavir/ritonavir was noninferior to lopinavir/ritonavir in achieving plasma HIV-1 RNA fewer than 400 copies/mL at 48 weeks.[12–14]

Darunavir is a substrate and inhibitor of CYP3A, which means it can boost serum concentrations of other medicines metabolized by this enzyme, and it may be impacted by inducers or inhibitors of its own metabolism. It's given with meals to treatment-experienced patients as a 600 mg tablet twice daily with 100 mg ritonavir or as an 800-mg tablet once daily with 100 mg ritonavir for patients with no genotypic darunavir resistance mutations. In treatment-naive patients, a once-daily dose of 800-mg /100-mg darunavir/ritonavir was well tested.[15–18]

In Ethiopia, there is a growing tendency of enrolling clients in second-line regimens as a result of greater access to ART and frequent viral load monitoring. Similarly, data from the viral load monitoring program revealed an increase in the number of second-line ART patients with an uncontrolled viral load. As a result, in August 2018, the Federal Ministry of Health approved and deployed Darunavir/ritonavir-based third-line antiretroviral therapy.[5,6]

As of September 2018, 13,507 clients were on second-line therapy, accounting for 3.2% of all ART patients. Despite the scarcity of data on second-line treatment failure, data from the Ethiopian Public Health Institute's (EPHI) national routine viral load program revealed that 40 of 198 (20%) patients on second-line had viral loads greater than 1000 copies/mL.[6]

According to a multicenter study conducted in Northern Ethiopia, the failure rate of second-line treatment was found to be 72.3% per 1000 person years (95% confidence interval: 55.75–93.71).[19]

Ethical Review

After obtaining permission from the Hawassa University Institutional Review Board, the patient provided written informed consent for the publication of this case report (IRB).

Case Presentation

This is a case of a 40-year-old female known HIV/AIDS patient who has been on ART for the last 14 years with good adherence and regular follow-up, and who is now on 3rd line ART medication with TLD+DRR/r (on her 11th month) after being diagnosed with second-line treatment failure.

After 6 months and 1 week of therapy, the viral load (VL) was sent, and the result was undetectable. The CD4 cell count is currently 950 cells/mm^3. The patient's clinical conditions had greatly improved. She was on second line ART with TDF/3TC/LPV/r since 21/8/2019 with good adherence and follow up for one year prior to the current regimen.

She was on AZT/3TC/NVP at the start of ART (since 18/7/2006), with good adherence and regular follow-up. The CD4 and VL baseline levels were 52 cells/mm3 and 129,988 copies/mL, respectively. When she was switched to the second line, her CD4 and VL levels were 15 cells/mm3 and 98,136 copies/mL, respectively. Prior to one year before treatment failure, both were non-revealing, with the lowest CD of 570 cells/mm3 and the highest VL of 270 copies/mL. To put it another way, there have been no problems with treatment failure in the last 12 years, with all virologic and immunologic results falling within acceptable ranges.

She was acute on chronic sick looking when she arrived, and all of her vital signs were within normal ranges. Her height was 160 cm, her weight was 38, and her BMI was 14.8 kg/m2.

The pertinent findings were as follows: CBC=WBC=2.2103 with Neutrophil of 87.1, and Lymphocytes of 3.4, Eosinophil of 0.3 and Basophil of 0.3%, Haemoglobin=7 mg/dl, and Haematocrit=22%, and

the Platelet count was 66, 000, and the conclusion is Pancytopenia, and the Stool Examination re Modified Acid Fast Bacilli was also performed, and an oocyte of *C. parvum* was noticed (treated).

With this, she was managed for medical complications and was linked to an ART clinic, where her regimen was changed to TLD+ DRV/r with the diagnosis of second-line treatment failure and she was seen after two weeks, and she was fine, and she was seen again after a month with strict adherence. She took her medication monthly for the first month, then every three months after that.

Currently on third-line ART with TLD plus ritonavir-boosted darunavir, the VL is undetectable, and the CD4 count is 950 cells/mm3.The complete blood count (CBC) parameters were also checked, and they were all within acceptable bounds.

Clinically, she is doing a lot better than she was before, and she is now a determined and upbeat client who has an appointment at our hospital every three months.

She is the mother of three children, the oldest of whom is 21 years old and the youngest of whom is 8 years old, and all of her children have negative RVI (Retroviral Infection) serostatus. Her husband is also an RVI patient who takes his medication on a regular basis and has a viral load that is undetectable. They work as elementary school teachers and claim that their monthly salary is sufficient to support their family.

Discussion

To prevent HIV disease progression and the emergence of drug-resistant virus, the standard of care in HIV management is to suppress plasma HIV RNA as much as possible. Achieving virologic suppression in HIV-infected patients with drug-resistant virus can be difficult; however, advances in drug development have allowed for significant progress in the treatment of this patient population, even among those who have resistance to one or two classes of antiretroviral agents.[20]

Patients who have been diagnosed with second-line failure should be started on third-line therapy. The treatment goal for patients with drug-resistant viruses who have failed multiple regimens remains to reduce the viral load to below the detection level, or, if this is not possible, to the lowest level possible. Based on this case, we believe that combining TLD with ritonavir-boosted darunavir (DRV/r) for patients experiencing second-line ART virologic failure is typically recommended. However, because this is most likely a last resort, the issue should be discussed with an experienced HIV care and treatment physician as well as the patient. In this particular case, there were no adherence issues, and she was actually motivated to be put on this regimen after extensive discussion with the care provider. Before switching to a third-line regimen, it is best to check for adherence and patient readiness to ensure the desired outcome, undetectable viral load.[6,12–14,21–23]

Because of the presumed potency of this new generation PI, the managing team had high hopes for a suppressed viral load in this patient, which was met. Because genotyping is not available in our setting, the NRTI regimen combination is continued, and a pharmacologically boosted PI is used as the third agent. In this case, the selection of NRTIs is based on convenience and tolerability rather than resistance patterns. This is exactly what we did in this particular case. According to various sources, pharmacologically enhanced darunavir is preferable to lopinavir/ritonavir when it comes to tolerability and efficacy.[5,6,9,10,24–26]

Transitioning to this new regimen, on the other hand, necessitates careful clinical and programmatic considerations because Darunavir has been linked to serious side effects such as dyslipidaemia,[27] cholestatic hepatitis,[28] and peripheral neuropathy.[29]

According to new research, ritonavir-boosted darunavir can now be used as a first-line protease inhibitor in patients starting antiretroviral therapy and meeting the criteria for second-line treatment failure. It's critical to monitor the safety and efficacy of this newly initiated ART regimen in our patients.[6,24,26]

Conclusion

Third-line ART therapy, which was once thought to be a salvageable treatment, is now the primary option for second-line ART failure. TLD in combination with ritonavir boosted Darunavir is found to be effective at lowering viral loads in the blood below detectable limits. Even though there is paucity of data with the use of 3rd line ART regimen in Ethiopia, access to 3rd line ART containing ritonavir-boosted darunavir is advised because it has been found to be an effective alternative for patients who have failed second-line ART. We recommend that more research be done with a larger sample size, and that the findings in this paper be used with caution.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest for this work.

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