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Transitioning and Sequencing Paediatric Antiretroviral Treatment Regimens in the Dolutegravir Era: Emerging Questions and Considerations

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Abstract

For patients failing a dolutegravir (DTG)-based regimen, understanding a patient's personal history of antiretroviral (ARV) exposure will become increasingly important. With the universal initiation and switch to DTG-based regimens for currently stable patients, the terminology of first-, second- and third-line antiretroviral therapy (ART) is no longer applicable. The adoption of a patient centric approach will ensure that patients receive the most appropriate regimen to achieve virologic suppression. This article proposes a few recommendations for adopting a patient-centric approach to HIV treatment.

Keywords: ARV • Darunavir • Dolutegravir • Switching • Patient-centric • Treatment sequencing

Introduction

The clinical benefits of dolutegravir (DTG) containing antiretroviral treatment (ART) for people living with HIV (PLHIV) are well documented [1]. The 2021 WHO Consolidated HIV Guidelines clearly outline the approach to treatment of newly diagnosed patients and patients on regimens lacking DTG [2]. Simply, DTG is recommended for all, as a preferred agent for first- and second-line ART. With the introduction of paediatric DTG (pDTG) formulations, national AIDS control programmes are poised to proceed with DTG, as an anchor ARV of first- and second- line ARV regimens across all weight bands for children living with HIV (CLHIV) (except neonates). Irrespective of current regimen, protease inhibitors (PI) can be reserved only for situations where DTG-based regimens are not tolerated [2-4].

Building on the success of the public health approach, this manuscript offers thoughts on ART sequencing with a patient-centered approach. Considerations are offered to assist AIDS control programmes with updates to national HIV treatment guidelines focusing on appropriate sequencing of ARVs, to optimize clinical outcomes [5,6].

The introduction of DTG-based regimens and the departure from non-nucleoside reverse transcriptase inhibitors (NNRTIs)- and lopinavir/ritonavir (LPVr)- based regimens in low and middle income countries (LMIC) has the potential to enable programmes to depart from ARV class-based sequencing of regimens.

PLHIV may be taking a regimen containing dolutegravir, lamivudine, tenofovir as a first-line or second-line – or as a component of a third line regimen with additional ARVs [7]. Now, clinicians can manage patients who are eligible for DTG in the absence of a complete medication history, virologic suppression history, and resistance test results. For patients failing a DTG-based regimen, however, understanding an individual's personal history of ARV exposure will become increasingly important. Scale up of electronic medical record systems that capture and allow easy retrieval of personal ARV history will be required as LMIC move towards an approach of individual patient management with DTG-based ART failure.

Discussion

Below are frequently asked questions with considerations which may be useful to guide national AIDS control programmes in drafting guidelines and clinicians in applying a patient-centered approach to treatment.

How does the designation of first-, second-, or third-line impact the feasibility of transitioning to a DTG based regimen?

To date, switching of a patient from a first-line regimen to a second-line regimen has typically required discontinuation of two out of three ARVs, and initiation of two new ARVs, following confirmed virologic failure and failure of adherence interventions. With the universal initiation and switch to DTG-based regimens for currently stable patients (and the potential introduction of dual oral ART and long-acting injectable ART), the terminology of first-, second- and third-line ART is no longer appropriate. Additionally, the transition of virologically suppressed patients from one regimen to another does not neatly fit within the first-, second-, and third- line structure. As ART regimens have historically increased in efficacy, the need for reserving potent ARVs, such as ritonavir boosted darunavir (DRVr), for third-line treatment becomes obsolete, because of the high likelihood of suppression with initial regimens for life. When patients do not respond to DTG, DRVr should be the preferred protease inhibitors (PIs). Preference for DRVr over other PIs is based on trials exhibiting high efficacy of DRVr, despite a fully compromised backbone, lower risk of virologic failure and lower rates of treatment discontinuation when compared to other boosted PIs [8,9]. The once daily dosing of DRVr is for PI-naïve patients and can be considered for PI-experienced patients, who have drug resistance testing results indicating a lack of DRVr associated resistance mutations [10]. Whether treating with pDTG, DRVr or future products, clinicians should focus on providing the best regimen available for their patient, irrespective of treatment sequencing.

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Is drug resistance testing recommended before transitioning to DTG, for a patient who is failing therapy?

Drug resistance testing is not routinely considered a prerequisite for transition, further challenging the definition of second- and third- line ART. Evidence from the NADIA trial proves the non-inferiority of tenofovir disoproxil fumarate (TDF) compared with zidovudine (AZT) when combined with DRVr or DTG in patients who have previously failed on a regimen containing TDF. One of the strengths of the NADIA trial was the lack of use of resistance testing when determining regimens for each subject, using an approach that can be used in LMIC. WHO recently endorsed an approach for PLHIV who are currently on a non DTG based regimen, with clinical or immunological failure to switch to TDF or AZT with 3TC and DTG [2,3].

How should clinicians proceed in finding appropriate regimens when patients fail DTG?

Lack of generic formulations of DRVr should not be a barrier to considering DRVr for immediate use, after confirmed DTG failure. Particularly for CLHIV without prior PI exposure, transitioning directly from DTG-based regimen to DRVr-based ART offers an option of once-daily dosing (compared to twice-daily LPVr) and stronger protection from acquisition of additional resistance mutations (compared to ATVr) [11]. Furthermore, switching of individual NRTI for an optimized backbone following virologic failure with NNRTI- and PI-based regimens may not be warranted when introducing DTG or DRVr as an alternative regimen in CLHIV [9,12].

Conclusion

A thoughtful approach to the continued scale up of DTG-based ART for all populations, will ensure its positive impact is maximized. The considerations in this paper can assist national policy-makers and frontline health practitioners in anticipating uncertainties and addressing them in a data-informed manner. Now is the time to treat HIV in the same way a clinician approaches treatment of other chronic health conditions, such as hypertension and hyperlipidemia, where the switch to the more tolerable and efficacious treatments is guided by clinical and laboratory parameters in the absence of delineating regimens as first, second, or third line.

Competing Interests

The authors declare no competing interests.

Authors' Contributions

The initial concept for this short report was conceived by AG and CYM. AG and CYM contributed to the initial composition. CYM drafted the initial outline for the manuscript. All authors (JMS, AG, NYR, CYM) reviewed and approved the final content prior to submission.

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