National Essential Medicine List
Paediatric Hospital Level Medication Review Process
Component: HIV

MEDICINE REVIEW
TITLE: Dolutegravir in children (3kg and over 4 weeks to 20kg)
DATE: May 2022

1. Executive Summary:

Date: January 2022
Medicine (INN): Dolutegravir (DTG), oral dispersible tablet
Medicine (ATC): J05AX12
Indication (ICD10 code): B24
Patient population: Children living with HIV 3kg and over 4 weeks to 20kg
Prevalence of condition: over 320 000 children aged 0-14 years infected with HIV.[1]
Level of Care: Primary
Prescriber Level: Nurse
Current standard of Care: First-line therapy: Abacavir + Lamivudine + Lopinavir/Ritonavir (DTG to replace Lopinavir/ritonavir)

- **Efficacy estimates: (preferably NNT):** Superior efficacy shown for DTG vs standard of care. Difference in failure by 96w (DTG-SOC) -8% (95% CI: -14% to -3%). NNT: 12

Motivator/reviewer name(s): Paediatric Expert Review Committee

Key findings

- Dolutegravir based ART regimen is associated with superior viral load (VL) suppression when compared to Lopinavir/ritonavir based ART for children either starting ART or switching to a second line regimen.
- Available data now demonstrates this in children in weight band 3kg to 20kg.
- A DTG based ART regimen simplifies the paediatric ART dosing regimens.

PAEDIATRIC EXPERT REVIEW COMMITTEE RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option or to use the alternative **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
					X

Rationale: Dolutegravir based ART regimen is associated with superior VL suppression when compared to Lopinavir/ritonavir based ART for children either starting ART or switching to a second line regimen.

Level of Evidence: LoE I

(Refer to appendix 1 for the evidence to decision framework)

BACKGROUND

Dolutegravir has been included as part of antiretroviral (ART) regimens in adults and children 20kg and over in the South African HIV Guideline. [2] Dolutegravir 10 mg scored dispersible formulation has been submitted to the South African Health Products Regulatory Authority (SAHPRA). This formulation will allow for dolutegravir to be used in children under 20 kg.

RESEARCH QUESTION: Should Dolutegravir be used in first and second-line ART regimens in children under 20 kg.

METHODS

Eligibility criteria for review

Population: HIV infected Children, 3 kg to 20 kg
Intervention: Dolutegravir (DTG)
Comparators: Standard of Care (Lopinavir/Ritonavir)
Outcomes: Virological or clinical failure by 96 weeks
Study designs: Randomised Non-Inferiority Trials

RESULTS

Identification of studies

The ODYSSEY trial was designed to compare the efficacy and safety of dolutegravir-based ART to standard of care in children and adolescents who were starting first- or second-line ART. The main trial[Error! Bookmark not defined.] was included children and adolescents who were at least 14 kg, while a separate cohort looked at those less than 14 kg.[Error! Bookmark not defined.]

Description of studies

Turkov et.al. ODYSSEY Trial Team, 2021[3]

- Open-label, randomised, non-inferiority trial comparing 3-drug ART including dolutegravir or standard of care (non-dolutegravir based ART) in children and adolescents starting first- or second-line ART. (n = 707)
- Primary endpoint: proportion of participants with virologic or clinical treatment failure by 96 weeks, as estimated by Kaplan-Meier method

ODYSSEY Trial Team. Conference presentation. 2021 (not yet published)[4]

- Additional cohort of the ODYSSEY Trial including children under 14 kg (n = 85), to confirm efficacy, safety and the most practical dosing.
- Aim to enrol ≥20 children in each of the three lower WHO weight bands: 3-<6kg, 6-<10kg and 10-<14kg.
- Proportions of first- and second-line not pre-specified.
- Primary outcome: the difference in the probability of clinical/virological failure by 96 weeks between DTG-based ART and standard if care in children <14kg.

Effect of Intervention

14 – 20 kg

- At 96 weeks, 47 participants in the dolutegravir group and 75 in the standard of care group had treatment failuare (estimated probability, 0.14 versus 0.22; difference, -0.08; 95% CI -0.14 to -0.03; P = 0.004)
- Treatment effects were similar with first- and second-line therapies (P = 0.16 for heterogeneity). A total of 35 participants in the dolutegravir group and 40 in the standard of care group had at least one serious adverse event (P = 0.53), and 73 and 86, respectively, had at least one adverse event of grade 3 or higher (P = 0.24). At least one ART-modifying adverse event occurred in 5 participants in the dolutegravir group and in 17 in the standard-care group (P = 0.01).

<14 kg

- Dolutegravir shown to be more favourable in term of virological or clinical failure, difference in proportion with virological or clinical failure by 96 weeks: Bayesian analysis: -0.106 (-0.192 to -0.020),

stand-alone analysis: -0.196 (-0.379 to -0.0005), pooled analysis (with ≥ 14 kg data): -0.094 (-0.146 to -0.038).

- No difference in adverse events.

CONCLUSION

It is recommended that dolutegravir be introduced into first and second line ART regimens for children from 3 to 20 kg.

Reviewers:

Dr M Archary and Dr J Riddin

Peer-reviewed: Paediatric Expert Review Committee as collective

Declaration of interests:

Dr M Archary: Principle investigator of P1093 and Odyssey trial (trial for DTG registration).

This interest was managed by the peer-review of the review and evidence by the Paediatric Expert Review Committee. Dr M Archary was not part of the drafting of the final recommendations.

Dr J Riddin: No interests to declare.

Paediatric ERC members (besides Dr Archary): No specific interests pertaining to this review to declare.

Table 1. Characteristics of included studies

Citation	Study design	Population (n)	Treatment	Primary outcome	Main findings	Risk of Bias
Turkov et.al. ODYSSEY Trial Team, 2021[3]	Open-label, randomised, non-inferiority trial	Children and Adolescents starting 1st or 2nd line ART, weighing at least 14 kg. *(not including ≤ 14 kg cohort)*	DTG-based ART or standard of care	Virological or clinical treatment failure by 96 weeks (as estimated by Kaplan-Meier)	At 96 weeks, • 47 participants in the dolutegravir group and 75 in the standard of care group had treatment failure (estimated probability, 0.14 versus 0.22; difference, -0.08; 95% CI -0.14 to -0.03; P = 0.004) • Adverse effects were similar with first- and second-line therapies (P = 0.16 for heterogeneity).	Overall LOW risk of bias Open-label study thus no blinding of participants and personnel
ODYSSEY Trial Team. Conference presentation. 2021 (not yet published).[4]	Randomised, non-inferiority trial	**Children ≤ 14 kg** starting 1st or 2nd line ART (n=85) • 3 - ≤6kg: 23 children • 6 - ≤10kg: 40 children • 10 - ≤14kg 22 children	DTG-based ART or standard of care	Virological or clinical failure at 96 weeks	• Superior efficacy shown for DTG vs SOC • Difference in failure by 96w (DTG-SOC) -8% (95% CI: -14% to -3%) • NNT: 12	• Not yet published: however same protocol as above

Appendix 1: Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High [x] Moderate [ ] Low [ ] Very low [ ] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	Randomised, non-inferiority trial data including participants from defined weight bands.
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large [X] Moderate [ ] Small [ ] None [ ]	Superior viral load suppression with DTG than LPV/r based regimens.
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High [x] Moderate [ ] Low [ ] Very low [ ] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	Randomised, non-inferiority trial data
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** **L**arge [ ] Moderate [ ] Small [x] None [ ]	Adverse events were similar in DTG and standard of care, with no safety concerns on DTG
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention [x] Favours control [ ] Intervention = Control *or* Uncertain [ ]	
FEASABILITY	**Is implementation of this recommendation feasible?** Yes [x] No [ ] Uncertain [ ]	Currently not registered with SAHPRA, however on registration no feasibility challenges anticipated
RESOURCE USE	**How large are the resource requirements?** More intensive [ ] Less intensive [ ] Uncertain [X]	No South African Market price to evaluate until registered.
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [X] Major [ ] Uncertain [ ] **Is the option acceptable to key stakeholders?** Yes [x] No [ ] Uncertain [ ]	Will simplify paediatric regimens
EQUITY	**Would there be an impact on health inequity?** Yes [ ] No [ ] Uncertain [X]	

REFERENCES

[1] World Health Organisation (WHO). South African Country profile. 2016. https://www.who.int/hiv/data/Country_profile_South_Africa.pdf

[2] National Department of Health. National Consolidated Guidelines: For the management of HIV in Adults, Adolescents, children and infants and prevention of mother-to-child transmission. October 2019.

[3] Turkova A, et.al. ODYSSEY Trial Team. Dolutegravir as First- of Second-Line Treatment for HIV-1 Infection in Children. NEJM. 2021, 385:2531-2543.

[4] ODYSSEY Trial Team. A randomised comparison of DTG-based ART vs Standard of Care in infants and young children living with HIV weighing 3 to 14kg: results from the ODYSSEY trial. Presented at 11th IAS (International AIDS Society) Conference on HIV Science, 18-21 July 2021.