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PENTA HIV FIRST AND SECOND LINE ANTIRETROVIRAL TREATMENT GUIDELINES 2019

Produced by the Penta HIV guidelines writing group on behalf of Penta

SCOPE OF GUIDELINE

This summary guideline outlines preferred and alternative treatment options for children living with perinatally acquired HIV, diagnosed before 18 years of age. The format and content of the full Penta HIV Treatment Guidelines are currently under review.[1]

WHEN TO TREAT

Penta recommends the initiation of antiretroviral therapy (ART) in all children diagnosed with HIV irrespective of age, CD4 count and viral load and emphasises the need for urgent diagnosis and treatment for infants born to women living with HIV.[2] Penta endorses the "U=U" campaign (undetectable = untransmissible).[3] This is particularly relevant to sexually active adolescents and is potentially a motivational message to enhance adherence and prevent onward HIV transmission.

WHAT TO START: FIRST LINE THERAPY

All first line and the majority of second line ART regimens currently include 2 nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) together with a drug from a different class (3rd agent). First line therapy in treatment naive children increasingly favours integrase strand transfer inhibitors (INSTI) or boosted protease inhibitors (bPI) with 2 NRTIs as preferred regimens from 2 weeks of age (Table 1). Although direct evidence from randomised controlled trials is awaited for children, evidence for non-inferiority or superiority of INSTIs compared to other classes of 3rd agents in adult patients is substantial.[4-7] Real life experience of using INSTIs in children is accumulating rapidly.[8] The results of the ODYSSEY trial comparing dolutegravir (DTG) in combination with 2 NRTIs to standard of care for first and second line therapy in children are expected in 2020 (ClinicalTrials.gov: NCT02259127).

Whilst "preferred options" are recommended, "alternative options" are acceptable and remain important choices in settings where ART availability is limited. Potential transmitted resistance and resistance resulting from maternal or infant antiretroviral exposure during failed prevention of vertical transmission should also be considered when choosing a regimen. For example, when nevirapine (NVP) has been used in pregnancy raltegravir (RAL) should be the preferred 1st line option in children <2 weeks of age. Whenever possible first line 3rd agents with high barrier to resistance have been selected in view of known difficulties with adherence in children and adolescents.

It should be noted that these guidelines include recommendations for use of some antiretrovirals outside their European licence. Local policy for the use of unlicensed medication should be followed. Apart from decisions on standard first line in high prevalence setting, options should be discussed within a multidisciplinary meeting (MDT)/paediatric virtual clinic (PVC). Adherence is key to achieving and maintaining viral suppression and adherence support and assessment should be provided at/prior to initiation of ART and at all subsequent visits. The use of peer mentors, where available, is recommended.

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Table 1. First line recommendations

	3rd Agent (in alphabetical order)		Backbone	
Age	**Preferred**	**Alternative**	**Preferred**	**Alternative**
0-2 weeks	NVP§	RAL***	AZT + 3TC	-
2 weeks – 3 years	*DTG*¶ LPV/r	NVP RAL	ABC* + 3TC**	AZT + 3TC** TDF + 3TC (from 2y)
3 – 6 years	ATV/r DRV/r *DTG*¶	EFV LPV/r NVP RAL	ABC* + 3TC	TDF + XTC AZT + XTC
6 – 12 years	DTG	ATV/r DRV/r EFV EVG/c RAL	ABC* + 3TC† TAF# + XTC	TDF + XTC
> 12 years	DRV/r/c‡ DTG	ATV/r/c‡ EFV^ EVG/c RAL RPV	ABC* + 3TC† TAF# + XTC	TDF + XTC

Notes:

* ABC should NOT be prescribed to HLA B5701 positive individuals (where screening is available).
** If using NVP as a 3rd agent in children aged 2 weeks to 3 years, consider using 3 NRTI backbone (ABC + AZT + 3TC) until VL consistently <50 copies/ml
*** In settings with high risk of transmitted NVP resistance and restricted access to integrase inhibitors in appropriate infant formulations, LPV/r can be considered (with appropriate monitoring) for infants under 2 weeks.
† at HIV VL > 100,000 c/ml ABC + 3TC should be combined with DTG as 3rd agent.
‡ at time of writing DRV/c and ATV/c FDCs are not licensed for 12-18 years of age however their constituent parts are licensed in other formulations. DRV/c and ATV/c FDC are therefore included as 1st line options.
§ If starting NVP in infant under 2 weeks, it is acceptable to subsequently continue with NVP or switch to LPV/r once older than 2 weeks
¶ DTG is soon to be licensed in younger ages. Once licensed this should be the preferred option in younger children and bPIs should move to alternative 3rd agents

[#] TAF is only licensed for treatment of HIV in combination with FTC
[^] EFV 400mg dose is not presently licensed in Europe. In settings where it is available it may be considered as an alternative 1st line 3rd agent acknowledging that data supporting efficacy in adolescents is limited.

Simplification Strategies
As children age and grow on suppressive ART, consideration should be given to simplification to robust once daily low pill burden regimens with optimal toxicity profiles. In children aged less than 3 years commenced on liquid ritonavir boosted lopinavir (LPV/r), consider switching to once daily INSTI or bPI based regimens when pill swallowing achieved. Simplification to bPI monotherapy and treatment interruptions are not recommended. Robust randomised trial evidence supporting the routine use of dual therapy in first and second line therapy for children is awaited.

Special Populations
Seek specialist expert advice e.g. through a PVC.

1. **Adolescent girls of child bearing potential:** reports of a possible increase in neural tube defects in women who conceived on DTG based regimens require further clarification.[9,10] Until more data becomes available DTG containing regimens should only be prescribed with careful counselling around contraception. For regimen selection in pregnancy refer to local HIV in pregnancy guidelines (e.g. European AIDS Clinical Society (EACS), British HIV Association (BHIVA))
2. **Hepatitis B co-infection:** requires an ART regimen that includes TAF or TDF in the NRTI backbone.
3. **Hepatitis C (HCV) co-infection:** seek specialist advice for consideration of curative HCV therapy for children and adolescents with HCV co-infection.
4. **TB co-infection:** EFV is the preferred choice for co-administration with TB therapy that includes rifampicin (**twice daily** DTG with rifampicin is used in adult patients, data in children is pending (ClinicalTrials.gov: NCT02259127)). For under 3 years **super boosted** LPV/r should be considered,[11] specialist advice should be sought with therapeutic drug monitoring recommended where available.

VIROLOGICAL FAILURE: WHAT TO SWITCH TO – SECOND LINE ART
Virological failure (defined as 2 consecutive VL >400 c/ml) is almost always due to suboptimal ART adherence, and always requires adherence assessment and support. Resistance testing is recommended where possible. Choice of second line therapy is dependent both on previous antiretroviral exposure and documented HIV-1 resistance mutations. Second line options should ideally be discussed at a PVC/MDT, especially if resistance has been found.

Choosing a 3rd agent:

Failed on first line NNRTI
- Switch to bPI or DTG (where licensing allows) with optimised 2 NRTI.
- If high VL and extensive resistance impacting on NRTIs consider using regimen with at least 3 active drugs (e.g. INSTI with bPI and 2 NRTI)
- Consult with MDT/PVC).

Failed on first line bPI

- If no significant resistance to protease inhibitors, continue bPI (consider switch to DRV/r) with optimised 2 NRTI with adherence support
- consider switch to INSTI with high barrier to resistance
- consider INSTI or PI based single tablet FDC with 2 NRTI to lower pill burden (e.g. DRV/c, DTG or BIC where/when licensing allows)

Failed on first line INSTI

- Switch to bPI or if resistance testing demonstrates no INSTI resistance, switch to/continue DTG with optimised 2 NRTI
- If INSTI resistance and substantial NRTI resistance, discuss at PVC/MDT to consider initial therapy with INSTI + bPI + optimised 2 NRTI.

Optimising NRTI backbone

- If resistance testing available use results to guide choice of 2 NRTI
- If NRTI resistance is demonstrated, XTC with either TAF or TDF or AZT are the preferred options, used according to license, ensuring at least one active NRTI
- If resistance testing not available, switch to (or continue) TDF or TAF or AZT with 3TC or FTC (see below rationale).

If failed on ABC + 3TC (and in absence of K65R), switch to TDF or TAF or AZT (if contra-indication for TDF or TAF) with XTC is recommended. It is well established that M184V (a common mutation arising when failing on 3TC/FTC) causes high level resistance to both FTC and 3TC. However ongoing use of either FTC or 3TC is still recommended in the presence of this mutation as it is associated with an increased susceptibility to tenofovir and AZT.

Subsequent virological failure on 2nd line therapy requires further assessment of adherence and resistance testing, if available. Therapeutic drug monitoring may be useful if concerned about subtherapeutic drug levels.[12] Choice of subsequent regimens should be made through an MDT/PVC. ART should continue despite virological failure (ideally with a robust bPI based regimen including XTC) to maintain CD4 count whilst additional adherence support is provided.

References

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Abbreviations:
3TC= lamivudine
ABC= abacavir
ATV= atazanavir
AZT= zidovudine
BD= twice daily
BIC= bictegravir
bPI= boosted protease inhibitor
/c= cobicistat-boosted
EFV= efavirenz
EVG= elvitegravir
FDC= fixed dose combination
FTC= emtricitabine
DRV= darunavir
DTG= dolutegravir
INSTI = integrase strand transfer inhibitor
LPV= lopinavir
MDT= multidisciplinary team
NNRTI= non-nucleoside reverse transcriptase inhibitor
NRTI= nucleos(t)ide reverse transcriptase inhibitor
NVP= nevirapine
/r= ritonavir-boosted
PVC= paediatric virtual clinic
RAL= raltegravir
RT= reverse transcriptase
TAF= tenofovir alafenamide
TDF= tenofovir disoproxil fumarate
XTC = lamivudine or emtricitabine

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