

Second-line ART

Recommendations

1. A boosted PI + 2 NRTIs are recommended for 2nd-line ART. (Strong recommendation, moderate quality of evidence)
2. ATV/r and LPV/r are the preferred boosted PI options for 2nd-line ART. (Strong recommendation, moderate quality of evidence)
3. TDF+3TC or FTC and AZT+3TC as the preferred NRTI backbone options for 2nd-line ART. (Strong recommendation, moderate quality of evidence)
4. Heat stable, fixed-dose combinations or co-packaged formulations are recommended wherever possible. (Strong recommendation, high quality of evidence)

Domains and considerations

Quality of evidence

On the question of whether **3TC should be maintained** in second-line regimens, five trials (3 RCTs) have addressed the impact of retaining 3TC in 2nd-line regimens (Castagna, Eron, Campbell, Fox and Hull). In the GRADE profile, the quality of evidence is low for 4 of the 5 trials (Hull is not included in the profile) and the effect size is moderate for the non-critical outcomes of the proportion of patients achieving VL suppression and the mean reduction in HIV RNA from baseline, supporting conditional recommendation to retain 3TC in 2nd-line regimens for its impact on viral fitness. If the recommended sequencing of NRTIs is followed (AZT+3TC in 1st line is followed by TDF +3TC in 2nd-line and TDF+3TC is followed by AZT+3TC in 2nd-line), then 3TC is maintained by default.

On the question of whether **PI monotherapy** be used as second-line ART, there is moderate quality of evidence from 9 RCTs showing less virological suppression (<50 copies/ml) for PI monotherapy compared to standard triple ART regimens. There were no other significant differences in critical or important outcomes (very low to moderate quality evidence), although non-critical outcomes, such as grade 2 adverse events and lipoatrophy, were not captured in the GRADE table. Further, there is evidence from individual trial reports of higher rates of viral rebound in patients on monotherapy compared to combination ART. All but two studies (Cameron 2008 and Delfraisy 2008) enrolled ART-naïve patients and/or patients with VL suppression. Hence, the GRADE profiles were downgraded for serious imprecision and indirectness. Current PI monotherapy data are insufficient to suggest that NRTIs should not be retained in the regimen.

On the question of **which boosted PI (bPI)** should be used in second-line therapy, there is moderate quality of evidence that ATV/r is non-inferior to LPV/r (in combination with TDF and an optimized second NRTI) in treatment experienced patients, (Johnson 2005, Johnson 2006). Imprecision and indirectness were reported in the GRADE table with patients being two-regimen experienced. There is low-moderate quality evidence that FPV/r, ATV/r and DRV/r are non-inferior to LPV/r in ART naïve patients (Castle, Klean and Artemis studies). Non-serious adverse events varied by boosted PI with no significant difference in serious adverse events (very low quality evidence). All unboosted PIs (including NFV and ATV) are considered inferior to bPIs.

On the question of which **NRTI backbone** to use in 2nd-line therapy, very few studies of relevance were identified. The recommended NRTI sequencing is based on likely resistance mutations and

potential for retained antiviral activity in the two scenarios of early and late diagnosis of failure and switching (Elliot 2008). If AZT+3TC is used in 1st-line with sensitive monitoring and a low switch threshold, (M184V mutation common, TAMS less common), the NRTIs with remaining activity are TDF and ddI, (both very likely), ABC (likely), with likely benefit from 3TC. In the scenario of intensive monitoring and high switch threshold, (M184V, TAMS common, K65R rare but possible), TDF and ddI activity are less likely, AZT and ABC unlikely, with benefit from 3TC less likely.

If TDF +3TC are use in 1st line, with sensitive monitoring and a low switch threshold, (M184V common, K65R possible), the NRTIs with remaining activity are AZT and d4T (very likely), ddI, ABC, TDF (possible) with likely benefit from 3TC. In the scenario of intensive monitoring and high switch threshold, (M184V, K65R common), activity of AZT and d4T is very likely, activity of ddI, ABC and TDF unlikely with likely benefit from 3TC.

No uncertainty about the current quality of evidence on the efficacy of bPIs

Uncertainty about the current quality of evidence about which NRTIs should be used but studies are ongoing

Risks/Benefits

Benefits

- Simplification of therapeutic options
- Simple procurement as the preferred NRTIs are included as 1st-line regimens
- Reduction of pill burden (some combinations can be used once daily)
- Possible benefit in patients with HBV infection, especially if combined with TDF in 2nd-line
- Reduced chance of hepatic flare associated with stopping 3TC in patients with HIV/HBV co-infection
- 3TC has good safety profile and few side effects
- Limiting use of ABC and ddI as second line NRTIs will reduce complexity and cost

Risks

- Some countries have chosen alternate bPIs already (IDV/r, SQV/r, FPV/r)
- Confusion may arise because 3TC is recommended in 1st-line and 2nd-line

Benefits outweigh risks

Values and acceptability

- PLHIV want simpler, better and more user-friendly 2nd-line options
- Program managers want simpler and clearer 2nd-line choices
- Physicians are comfortable with the evidence of some benefit and the safety profiles of 3TC
- PLHIV are comfortable with 3TC
- Clinicians may not be comfortable with not replacing all drugs (not feel comfortable recycling NRTIs)

Cost

- Cost containment by limiting choices and promoting use of FDC
- Generic heat stable LPV/r in the market already
- Co-blistered generic heat stable ATV and RTV in the market already
- Generic heat stable FDC of ATV/r in the pipeline and expected 2010 (co-blisters with TDF+3TC)

Feasibility

- Feasible with drugs readily availability in ART programs
- Generic formulations widely available
- Preferred bPIs are available in most countries
- A majority of country guidelines recommend 2nd-line ART be available
- Simplified procurement: the NRTIs recommended in 2nd-line are also used in 1st-line (in different combinations) and should be purchased by all national HIV/AIDS programs
- Other alternative bPIs (SQV, IDV, FPV and DRV) not available as FDC and more expensive than preferred options. SQV has a high pill burden, IDV has a high toxicity risk and FPV has a high cost

Gaps, research needs, comments

Ongoing studies

SECOND-LINE (48 sites: LPV/r+2 NRTIs vs. LPV/r+RAL), **2LADY** trial (Burkina Faso, Cameroon, Senegal- LPV/r+TDF+FTC vs. LPV/r+ABC+ddl vs. DRV/r+TDF+FTC, **EARNEST** trial (Malawi, Uganda, Zimbabwe: LPV/r vs. LPV/r+RAL vs. LPV/r+ 2 NRTIs, **SARA** trial (Uganda, Zimbabwe: LPV/r vs. LPV/r-based ART, **HIVSTAR** (Thailand: LPV/r vs. LPV/r+TDF+3TC or FTC)

Final comment

Strong recommendation

In developing these recommendations, the panel placed high value on simple 2nd-line regimens and availability of heat stable FDCs.