

When to switch ART

Recommendations

1. Where viral load (VL) is available for routine use, it is recommended to use it every 6 months to detect viral replication. (Conditional recommendation, low quality of evidence)
2. When VL is available, it is recommended to use it in a targeted approach to confirm clinical and/or immunological failure. (Strong recommendation, low quality of evidence)
3. The VL threshold for detection of treatment failure should be persistent > 5,000 copies/ml. (Conditional recommendation, low quality of evidence)
4. When VL is not available, it is recommended that immunological criteria for failure be used to confirm clinical failure. (Strong recommendation, moderate quality of evidence)

Domains and considerations

Quality of evidence

This review focused on improving the sensitivity and specificity of the current WHO clinical, immunological and virological definitions of failure by combining the criteria as follows.

1. Clinical versus immunological and clinical monitoring
2. Clinical versus virological, immunological, and clinical monitoring
3. Immunological and clinical versus virological, immunological, and clinical monitoring

The GRADE profiles of the two major RCTs (HBAC and DART) confirmed the low quality of the current evidence, but the pooled analysis of the size effects suggests a trend towards a higher risk of disease progression or death when clinical monitoring is used compared with clinical-immunological monitoring (moderate quality) and also less chance to switch to 2nd-line ART in patients that used clinical monitoring only (low quality). The same trend was observed when clinical or clinical-immunological monitoring was compared to clinical-immunological-virological monitoring (low to very low quality).

Clinical vs. immunological and clinical monitoring. Based upon two randomized trials (HBAC 2008, DART 2009), clinical monitoring alone resulted in increased mortality (low-quality evidence), increased AIDS-defining illnesses and mortality as a composite endpoint (moderate), no difference in serious adverse events (low), and increased numbers of unnecessary switches (low) compared to immunological and clinical monitoring.

Clinical vs. virological, immunological, and clinical monitoring. Based on a single randomized trial, (HBAC 2008) clinical monitoring alone resulted in increased mortality (low), increased AIDS-defining illnesses and mortality as a composite endpoint (low), increased unnecessary switches (low), and no difference in virological treatment failures (low) compared to virological, immunological, and clinical monitoring.

Immunological and clinical vs. virological, immunological, and clinical monitoring. Based on a single randomized trial (HBAC 2008) immunological and clinical monitoring resulted in no difference in mortality (low), no difference in AIDS-defining illnesses and mortality as a composite endpoint (low),

no difference in unnecessary switches (very low), and no difference in virological treatment failures (low) compared to virological, immunological, and clinical monitoring.

On the question of **VL threshold**, there is evidence to support a threshold of 5,000 copies/ml to define failure in an adherent patient with no other reasons for an elevated VL (e.g., drug-drug interactions, poor absorption, and intercurrent illness), as this value is associated with clinical and immunological deterioration in some cohort studies (e.g., PLATO, ICONA). Data from observational studies demonstrated that programs with virological, immunological, and clinical monitoring switch therapy more frequently (very low), and earlier (very low), and at higher CD4 counts (very low) compared to programs with only immunological and clinical monitoring (ARTLINC 2006, 2008).

Systematic reviews on studies on ART switching strategies and treatment failure definitions have shown low quality of evidence, with high variability on studies, no long term data and are usually not focused on a public health approach, which makes it difficult to establish definitive recommendations on this topic for RLS.

Other Key Points

- Clinical, immunological and virological criteria are frequently dissociated in clinical practice
- It is uncertain if viral load monitoring affects critical outcomes
- Immunological failure, as a stand alone criterion, is not a good predictor of virological failure
- Virological monitoring strategies are associated with earlier and more frequent switching
- Treatment switching has occurred at lower than expected rates in RLS

Uncertainty about the quality of evidence

Benefits

- More accurate assessment of treatment failure
- Reduction in the delay in switching to 2nd-line regimen
- Targeted use of VL can reduce the possibility of unnecessary switching based on immunological/clinical criteria when patient has VL suppression
- Regular use of VL can reduce the risk of resistance and protect susceptibility to 2nd-line drugs and may also have impact on HIV transmission
- Improved failure diagnostic criteria will save the cost of expensive 2nd-line drugs by confirming that they are needed or not by VL testing

Risks

- The optimum threshold for defining VL failure in a public health approach is unknown
- There are limited data on diagnostic accuracy of VL in RLS
- Modelling data suggest no difference in critical outcomes in VL versus no VL scenarios

Benefits outweigh risks

Values and acceptability

- Physicians and PLHIV consider clinical and immunological monitoring insufficient to promote a timely switch and want VL monitoring.
- ART switching has occurred at lower than expected rates in RLS, and the limited use of virological monitoring has been identified as an important factor.
- Many countries are considering employing VL to optimize the use of expensive 2nd-line drugs. The same rationale applies if/when 3rd-line drugs are available.

Acceptable

Cost

- The initial and ongoing cost is high. Use of VL to confirm clinical-immunological switch (targeted approach) probably will cost less than routine use of VL monitoring.
- Quality assurance programs need to be implemented at VL facilities irrespective of the VL strategy adopted
- Unclear cost-effectiveness of different monitoring strategies

Uncertainty Yes**Feasibility**

- Central VL facilities with adequate specimen transportation from clinic to laboratory are feasible
- Point of care VL capacity in urban settings is feasible
- Point of care VL capacity in rural settings is likely to remain unfeasible with current technologies
- Targeted use of VL seems to be more feasible

Feasibility with targeted use of VL more feasible than routine VL**Gaps, research needs, comments**

- New and simplified CD4 and VL techniques (point of care, dipstick) will become more available in the next 3 to 4 years
- Feasibility of dried blood spot (DBS) for VL
- What is the optimal viral load threshold for ART switch?
- What is the best VL monitoring strategy: targeted or routine approach?
- What is the long-term impact of drug resistance development on critical patient outcomes?
- Need to simplify immunological criteria
- Is 30% drop from the peak CD4 count any better than 50% drop?
- Does CD4 <100 after many months in an adherent patient who is clinically well an indication of failure?
- List of OIs that define clinical failure should be revised. Should pulmonary TB be considered as a criterion for ART switching?
- Role of Centers of Excellence/Switch Committees

Final comment

Strong recommendation

In developing these recommendations, the panel placed high value on the significant limitations of clinical and immunological monitoring for diagnosing treatment failure, the need to optimize virological monitoring, and ensure adherence