

## ART laboratory monitoring: Guiding principles

1. Laboratory monitoring in patients who do not yet need to initiated ART
  - With most patients still presenting for the first time with CD4 counts  $<200$  cells/mm<sup>3</sup> (in both resource limited and developed country settings), earlier identification of HIV status though expanding VCT and PITC is critical
  - Patients who are not yet eligible for ART should have CD4 count measurement (if available) every 6 months and more frequently as they approach the threshold to initiate ART.
2. Laboratory monitoring for ART efficacy
  - Laboratory monitoring is not a pre-requisite to the initiation of ART
  - Viral load is not necessary in deciding when to start ART
  - For patients receiving ART, monitoring of CD4 cell counts (if available) is recommended every 6 months, or more frequently if clinically indicated
  - If resources permit, viral load may be used in patients receiving ART in a targeted approach to confirm suspected treatment failure based on immunological and/or clinical criteria
  - If resources permit, viral load may be used routinely every 6 months, with the objective of detecting failure earlier than would be the case if immunological and/or clinical criteria were used to define failure
  - VL testing may be introduced for specific target groups first, including those at high risk for failure, such as pregnant women with a past history of ARV exposure, those with prior ARV exposure who have discontinued due to loss to follow-up, those co-infected with HIV/TB, HIV/HBV and IDUs.
3. Laboratory monitoring for ART toxicity
  - As a general principle, symptom-directed laboratory toxicity monitoring is recommended
  - The inability to perform renal monitoring is not a barrier to TDF use
  - Renal monitoring (calculated creatinine clearance, eGFR) is recommended in patients receiving TDF, especially in patients with underlying renal disease, older age group, small body weight or other renal risk facts such as diabetes or hypertension. There is evidence that patients taking TDF and a bPI may experience greater median decline in eGFR than those taking TDF and a non-NRTI. eGFR should be monitored more closely when TDF is used with a bPI.
  - For patients receiving AZT-containing regimens, haemoglobin should be measured before initiation and then as directed by signs/symptoms. Patients receiving AZT-containing regimens and with low body weight and/or low CD4 cell counts are at greater risk for anaemia. Such patients should have routine Hb one month after initiating AZT and then at least 3 months of monitoring.
  - In patients with HIV/HCV co-infection, regular monitoring of hepatic enzymes after initiation is recommended if available

### Domains and considerations

#### Summary of evidence

#### Monitoring for efficacy:

Low CD4 counts, even with undetectable viral load, are associated with increased morbidity and mortality (AIDS-related complications and deaths, cardiovascular, liver and kidney disease and non-AIDS cancers) and complications (including IRIS on initiation or ART) providing impetus for earlier

initiation of ART.

In the **FIRST** study, regardless of viral load, incremental CD4 increases lowered the risk of AIDS-related diseases by 44% for each 100 CD4 cell increase and the risk of non-AIDS diseases by 14% for each 100 CD4 cell increase (Baker 2008). Limited data exist to support frequency of CD4 count monitoring.

While viral load is not a major factor in deciding when to begin treatment, it has value when monitoring patients on ART to detect early treatment failure and reduce the chances of resistance.

### **Monitoring for toxicity:**

#### **1. NVP toxicity in patients with higher or unknown CD4**

There is conflicting evidence on the safety of NVP in people with higher CD4 counts. The available evidence is largely based on retrospective reviews or open-label studies, with very few randomized controlled trials providing evidence and results should be interpreted with caution. While there is a good representation of studies in RLS, key recommendations regarding use of NVP and CD4 cell count are based on trials in a resource unlimited settings. Initiation of NVP in patients with higher CD4 counts and undetectable VL may be a safer option. HIV/hepatitis C co infection is associated with higher incidences of hepatic toxicity, NVP discontinuation and mortality.

#### **2. d4T in HIV+ pregnant women, particularly regarding the risk of lactic acidosis**

In a systemic review, 14 articles were identified on d4T-related lactic acidosis all were non-comparative single-arm studies and provided no data suitable for creating GRADE profiles. Four articles and 3 case reports were from RLS. One of the articles (Wade) and 2 of the case reports focused on pregnant women and no conclusions could be drawn regarding the occurrence of lactic acidosis in pregnant women using d4T.

In a systematic review of the efficacy and toxicity of standard d4T dose (30 mg BID weight unadjusted following the addendum to the 2006 guidelines) and reduced d4T dose (weight adjusted 30 mg BID >60 kg, 20 mg BID <60 kg), appears to support equivalent efficacy and better tolerability for 20 mg BID in patients <60 kg. Two retrospective studies with small numbers of patients assessed 20 mg BID irrespective of body weight but no clear conclusions can be made from these data.

#### **3. AZT-related anaemia and neutropoenia**

Lower body mass and CD4 cell count appear to be factors related to risk of developing anaemia (Ssali, Isaakidis). No conclusions can be drawn regarding the use of AZT in pregnant women and risk of anaemia or neutropoenia, given the lack of data.

#### **4. Tenofovir (TDF) renal toxicity (glomerular and tubular dysfunction) and osteopoenia**

In a systematic review, 16 articles were identified on TDF-related renal toxicity, two of which came from RLS. Three of the studies were suitable for entry into GRADE tables, see below following the overall summary. In summary, the cumulative incidence rate of nephrotoxicity was 1% to 4%, with an estimated rate of Fanconi syndrome of 0.5% to 2%. Gender, age and race have not been demonstrated to be associated with TDF-induced nephrotoxicity. A 2007 report of all post marketing adverse drug reactions up to April 2005 for 10,343 patients in developed countries (Nelson) using TDF reported that serious adverse renal events were observed in 0.5% of patients and graded elevations of serum creatinine were observed in 2.2% of patients. Risk factors for increased serum creatinine were concomitant nephrotoxic medications, elevated serum creatinine, low body weight, advanced age and lower CD4 cell count. The authors conclude that risk factors for nephrotoxicity can

be identified and may be useful in managing patients at risk. Gallant and Moore 2009 reported no differences in renal outcomes in patients who initiated treatment with TDF or an alternate NRTI. The studies used in the TDF GRADE analysis (with the exception of Squires) are either open-label or observational studies.

#### **5. EFV teratogenicity, hepatotoxicity and CNS adverse effects**

No consensus was reached on whether any change can be made to the recommendation that EFV **NOT** be used in the 1<sup>st</sup> trimester. Pregnancy should be excluded in women of child-bearing potential before initiating EFV. EFV appears to be safe in the 2<sup>nd</sup> and 3<sup>rd</sup> trimester with no increase in birth defects above background levels reported to pregnancy registers. In RLS, EFV-related hypersensitivity, rash and liver toxicity appear to be low and self-limiting. Symptom-directed laboratory monitoring of liver enzymes is recommended in patients receiving EFV.

#### **Risks/Benefits**

##### **Benefits**

- VL will result in more accurate and earlier diagnosis of treatment failure
- Regular pre-ART CD4 monitoring will reduce losses to follow-up with PLHIV waiting for ART and facilitate earlier ART initiate
- Will facilitate scale up of TDF as preferred 1<sup>st</sup>-line ARV
- Reduce unnecessary HB testing in patients on AZT with no clinical anaemia

##### **Risks**

- Uncertainty about the safety of TDF in some populations without renal screening and monitoring
- Benefits outweigh risks for recommendations on VL, HB and pre-ART CD4
- Need more information on TDF use without renal monitoring, to decide if benefits outweigh risks

##### **Benefits outweigh risks**

#### **Values and acceptability**

- Some physicians may be uncomfortable with recommendations on renal monitoring.
- Recommendations on VL, HB and pre-ART CD4 acceptable.
- Need more information on TDF use without renal monitoring.

##### **Uncertainty: Yes**

#### **Cost**

- Increased costs for VL, pre-ART CD4.
- Potential for cost saving with Hb (minor) and no renal monitoring.

##### **No uncertainty**

#### **Feasibility**

- Widespread use of TDF may only be feasible if renal screening and monitoring is either available or not a prerequisite.
- VL and CD4 feasible with adequate investment in infrastructure and training.
- Broadly feasible for VL, pre-ART CD4 and Hb.

##### **Uncertainty: Yes**

#### **Gaps, research needs, comments**

- Need more information on TDF use without renal screening and monitoring.

**Final comment**

**Strong recommendation**

In developing these recommendations, the panel placed high value on improving access to and monitoring of safer ARVs.