POLICY BRIEF

AIDS MEDICINES AND DIAGNOSTICS SERVICE

TRANSITION TO NEW HIV TREATMENT REGIMENS – PROCUREMENT AND SUPPLY CHAIN MANAGEMENT ISSUES

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World Health Organization

This policy brief provides advice on a phased approach to transitioning to new HIV treatment regimens, as recommended by the World Health Organization (WHO). The target audience includes implementing partners, antiretroviral therapy (ART) programme managers, procurement managers and other relevant parties. The ultimate purpose is to ensure a continuous supply of antiretroviral (ARV) drugs, and ensure rapid and efficient implementation of the new WHO ARV guidelines, with smooth transitioning to new recommended ARV regimens, while reducing the wastage or expiry of products that are no longer recommended.

Background

WHO's 2013 *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach* recommends a preferred treatment regimen of tenofovir (TDF) in combination with lamivudine (3TC) and efavirenz (EFV), or TDF with emtricitabine (FTC) and EFV, preferentially as a fixed-dose combination. Comparative systematic reviews showed that these two regimens are associated with less risk of severe adverse events and better virological and treatment response when compared with other once- and twice-daily options currently available. Evidence also indicates that EFV has superior efficacy and tolerability compared with nevirapine (NVP), including when combined with TDF and 3TC (or TDF and FTC) as a once-daily regimen. In addition, WHO recommends that countries should discontinue stavudine (d4T) as a preferred first-line option, because of its cumulative mitochondrial toxicity.

The implementation of these new recommendations implies transition of the nearly 1 million patients who still received d4T at the end of 2012 to TDF-based regimens. A decision on how to deal with the 2–4 million patients who received zidovudine (AZT)-containing regimens and the 4.6–5.8 million patients receiving NVP-containing regimens is needed. As has been seen with previous regimen changes, any major transition of patients is a significant undertaking that requires careful procurement and supply chain management planning, coupled with clear guidance to inform prescribing practices.

The recommendations in support of triple ARV therapy for all pregnant and breastfeeding women in the prevention of mother-to-child transmission, and adult treatment initiation at a CD4 count of 500 cells/mm^3 or lower, will also increase the demand for ARV medicines.

Challenges

There are three key challenges facing the supply chain with these new recommendations:

1. The currently approved* suppliers of fixed-dose combination formulations of TDF/FTC/EFV (TEE) and TDF/3TC/EFV (TLE) expect that their production capacity will be sufficient to satisfy the increased demand for those formulations in 2014, as new capacity to produce TLE and TEE was brought on line in 2013. However, in the short term, their supply is still constrained, as buffer stocks held by countries that switched to TDF-based first-line treatment have not yet been established.
2. At present, the order to delivery lead times for TEE and TLE formulations average 4–8 months, inclusive of manufacturing time and delivery to country.
3. Purchasers and implementing partners with patients on d4T-, AZT- and NVP-based regimens have stocks and orders in process that should be considered in the transition process to avoid occurrence of stock-outs, and also wastage or expiry of usable products.

* Either approved or tentatively approved by the United States Food and Drug Administration or prequalified by WHO.

UNITAID

PEPFAR U.S. President's Emergency Plan for AIDS Relief

The Global Fund To Fight AIDS, Tuberculosis and Malaria

WHO/HIV/2014.4

RECOMMENDATIONS

Programmes should plan carefully and discuss with their suppliers the pace at which increased quantities of TDF- and EFV-based product can be made available. This will require a graduated process of transition. To ensure that supply is available to meet anticipated demand, a phased programme is highly recommended.

Suggested approaches are:

[1] Initiation of new patients eligible for ART on a TDF-based regimen, with preference for the fixed-dose combinations of TLE or TEE.

[2] Transition of patients currently on d4T-based regimens to a TDF-based regimen:
- For patients with clinical evidence of d4T-related toxicity, immediately replace with TEE or TLE.
- For patients with evidence of treatment failure, shift to second-line treatment with TDF/3TC, or TDF/FTC plus lopinavir/ritonavir (LPV/r) or atazanavir/ritonavir (ATV/r), as recommended by the 2013 WHO guidelines.
- For patients with minimal or no d4T-related toxicity, replace the d4T-based regimen with TEE or TLE as soon as possible in a phased programme to enable use of current d4T stocks and orders. No new procurement orders of d4T-based formulations should be planned.

[3] Transition of patients currently on AZT- and/or NVP-based regimens to TEE or TLE should be done in a phased programme to enable use of current stocks and orders, and to take into account the speed at which increased deliveries of TDF products can be ordered and delivered. In practice, it is suggested that national ART programmes consider the following sequence:
- For patients with evidence of treatment failure, shift to second-line therapy with TDF/3TC (or TDF/FTC) plus LPV/r or ATV/r (with monitoring of renal function), as recommended by the 2013 WHO ARV guidelines.
- For patients with clinical evidence of AZT-related or NVP-related toxicity, immediately change to TEE or TLE. New procurement orders of AZT- or NVP-based formulations should be planned only in the context of alternative first-line and/or second-line therapy needs.
- For patients developing tuberculosis while being treated with AZT/3TC/NVP, switch to TLE or TEE immediately, as NVP is not recommended as a preferred option and using TEE or TLE reduces the pill count and increases adherence to HIV and tuberculosis treatments.
- For patients without toxicity or treatment failure, replace with TEE or TLE as soon as possible. AZT is also associated with mitochondrial toxicity that can emerge more slowly than with d4T. EFV has clinical superiority over NVP in terms of suppression of viral load and length of time to treatment failure; people taking an EFV-based regimen are also more likely to achieve virological success. In the absence of treatment failure, switching to regimens containing TDF and EFV is not detrimental from the perspective of HIV drug resistance development.

It should also be recognized that not all countries can transition at the same time or at the same pace. Other factors need to be considered. For example, in areas with a high prevalence of HIV-2 infection the procurement and use of two-drug fixed-dose combinations (TDF with 3TC, TDF with FTC, and AZT with 3TC) might still be a preferred option, as this provides flexibility to combine the nucleoside reverse transcriptase inhibitors backbone with protease inhibitors in first-line therapy for HIV-2 infected patients. Advice on these challenges, and on how countries and programmes can coordinate their transitions and product requirements, is available from:

- WHO: AIDS Medicines and Diagnostic Service. Contact Vincent Habiyambere (habiyamberev@who.int)
- United States of America Government: Supply Chain for Health Division, Office of HIV/AIDS at the United States Agency for International Development (USAID). Contact Christine Malati (cmalati@usaid.gov), Mike Hope (mhope@usaid.gov), or for questions USGTx@usaid.gov
- The Global Fund to Fight AIDS, Tuberculosis and Malaria. Contact Martin Auton (Martin.Auton@theglobalfund.org) or Ade Fakoya (ade.fakoya@theglobalfund.org)
- UNITAID. Contact Taufiqur Rahman (rahmant@unitaid.who.int).

Conclusions

Transition to the new regimens will ensure patients are receiving the most effective treatment. This transition can be achieved provided it is well planned and coordinated. It is recognized that full transition cannot happen in all countries and across all patient populations immediately, but the constraint on the supply side for the new TDF- and EFV-containing formulations has progressively become less critical. However, as their supply is still somewhat constrained, it is important to ensure that patients are not put at risk of a treatment interruption. To achieve a smooth transition in as short a time as possible, without treatment interruptions, significant cooperation and collaboration between programme managers and their suppliers is essential.

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