MEMORANDUM

From: Coordinator ATC
To: Suzanne Hill, PSM
Date: 25 November 2008

Our ref:
Attention: Director, HIV/AIDS
Your ref:
Through: 

Subject: Proposed Recommendations of PI list for the next revision of WHO Model list of Essential Medicines

In order to update the list of antiretrovirals recommended for treatment HIV-infected adults, adolescents and children at the current WHO Model List of Essential Medicines (EML), the Department of HIV would like to suggest the following inclusions and deletions for the next revision:

1) Nelfinavir (NFV)

Nelfinavir is still used very rarely as an unboosted PI in situations where cold chain is not available or where the heat-stable formulations of boosted PIs. It is currently included in the EML as 250 mg capsules for adults and adolescents, and as powder formulation for paediatric use (50 mg/g). WHO currently recommends the use of PIs boosted with low dose ritonavir. NFV cannot be pharmaceutically boosted with ritonavir, has a high pill burden and is less potent than the currently available boosted PI options. Furthermore, heat-stable formulation of LPV/r is becoming more available in non-industrialized countries, reducing the indications of NFV in these settings. In 2007, NFV was withdrawn from the market by Roche, which was the originator and main producer of this PI, thereby, compelling many countries to replace it by LPV/r or other boosted PIs.

The Department of HIV therefore proposes that all formulations of NFV be removed from EML.

2) Lopinavir+ritonavir (LPV/r)

WHO recommends LPV/r as one of the preferred PI options in 2nd line ART. It is currently listed on the EML as a 133.3/33.3 mg FDC soft gel capsules for adults and a paediatric liquid formulation (400/100 mg/5 ml). Recently, heat-stable formulations for adults and children (200mg/50mg and 100mg/25 mg FDC tablets, respectively) have become available that are regarded by stringent regulators as pharmaceutically equivalent. These new formulations offer significant advantages over the previous forms and are now replacing the old formulations in the majority of settings. However, despite a progressive replacement, a significant number of countries are still using the non-heat stable formulations.

The Department of HIV therefore proposes that LPV/r heat-stable formulations (200+50mg and 100mg+25mg) should be added and LPV/r gel capsule (133.33mg/33.33 mg) and syrup (400mg+100mg/5ml) formulations should be maintained in EML, as an alternative in settings where the heat-stable formulation is not available or until tablets have been replaced the old formulations in most markets.

3) Indinavir (IDV)

IDV is an effective PI but safety concerns related to the high incidence of nephrolithiasis associated with its use. An increased daily fluid intake is necessary to reduce the occurrence of these renal problems making this PI rarely indicated as a therapeutic option. In the current EML, IDV is available as 200mg, 333 mg and 400mg tablets. WHO guidelines recommend, in situations where it is used 800 mg of IDV with 100 mg of ritonavir twice daily. Recent studies suggest that lower dose of boosted IDV (400/100 twice daily) is equally effective and less toxic. If IDV is used, the 400 mg strength tablet seems the most suitable formulation to delivery this PI.

The Department of HIV therefore proposes that IDV 200 mg and 333 mg formulations should be removed from the EML. However, IDV 400 mg capsules should be maintained.
4) Saquinavir (SQV)

SQV is listed by EML as 200 mg hard gel capsule and has been frequently used with ritonavir in 2nd line regimens as an alternative PI, but as one of the few options in TB/HIV co-infected patients using rifampicin and if rifabutin is not available. Furthermore, the pill burden associated with its use is high and GI intolerance is elevated, making this option less attractive when compared with the majority of other boosted PIs. Nevertheless, a higher strength formulation (500 mg tablet) is available in some industrialized countries and is most suitable to be delivered, as significantly reduces the pill burden associated with its use, particularly in patients with TB/HIV co-infection.

The Department of HIV therefore proposes that SQV 200mg should be removed from the EML, and as a replacement, the inclusion of SQV 500 mg tablets should be considered, particularly for treatment of tuberculosis in HIV co-infected individuals in concomitant use of rifampicin and PIs.

5) Atazanavir (ATV)

Atazanavir is one of the preferred PI options according recent WHO recommendations (http://www.who.int/hiv/pub/meetingreports/art_meeting/en/index.html), but is not listed in the current EML. This PI should be taken once daily, only with low dose ritonavir, and has an improved safety profile when compared with other boosted PIs, particularly regarding the metabolic side effects. A recent clinical trial (CASTLE Study) demonstrated that boosted ATV was non-inferior to LPV/r and had more favourable effect on total cholesterol and triglycerides. A dossier supporting the application is being prepared to be submitted to the EML committee. Fixed dose combinations of ATV and low dose ritonavir for use in adults are under study (300/100mg and 150/50 mg heat-stable tablets).

The Department of HIV therefore proposes that ATV 100mg, 150 mg and 300 mg capsules should be included in the EML.

6) Ritonavir (RTV)

Ritonavir has been used in low dose (100 mg once or twice daily) as a pharmacological booster for the majority of PIs currently in use (with exception of NFV) and a heat-stable formulation become recently available. These new formulations offer significant advantages over the previous forms and will replace the old formulations in the majority of settings.

The Department of HIV therefore proposes that RTV heat-stable formulations for adults and children (100 mg and 25mg tablets, respectively) should be included and RTV gel capsule (100 mg) and syrup (400mg/5ml) formulations should be maintained in the EML, as an alternative in settings where the heat-stable formulation is not available or until the old formulations in most markets have been replaced with tablets.

7) Stavudine (d4T) 40 mg

In May 2007, WHO recommended that d4T 40 mg tablets should not be used anymore, even in patients with more than 60 kg, due to the elevated risk of mitochondrial toxicity observed with this strength, and also because the use of lower doses (30 mg twice daily) is associated with lower toxicity rates and maintenance of clinical and virological efficacy (http://www.who.int/hiv/art/ARTAdultsaddendum.pdf).

The Department of HIV therefore proposes that d4T 40 mg should be removed from EML.

8) Zidovudine + Lamivudine + Abacavir (AZT/3TC/ABC)

WHO recommends this ART regimen as an alternative option in situations when the use of non-nucleoside drugs (EFV and NVP) are contraindicated or are too complex to use, as tuberculosis and hepatitis co-infections, pregnant women with high CD4 cell counts, severe reactions to NNRTIs and HIV-2 infection. It is also available as a FDC. However, despite of adequate clinical and immunological efficacy, lower level of toxicity and minimal risk of drug interactions, this regimen has been considered virologically less potent than NNRTI and PI based regimens, particularly in patients with high baseline viral loads, which makes it as an alternative choice for initial therapy for the majority of situations.

The Department of HIV therefore proposes to include this FDC in the EML for specific situations.