Proposal: policy on fixed-dose combination products

Background

The 2001 'Procedure to update and disseminate the WHO Model List of Essential Medicines', Criteria for Selection, includes the following statement regarding fixed dose combination products (FDCs):

"7. Most essential medicines should be formulated as single compounds. Fixed-ratio combination products are selected only when the combination has a proven advantage in therapeutic effect, safety or compliance over single compounds administered separately. Examples of combination medicines that have met these criteria include new formulations for tuberculosis and malaria."

This was modified in 2005 to read:

"Most essential medicines should be formulated as single compounds. Fixed-dose combination products are selected only when the combination has a proven advantage over single compounds administered separately in therapeutic effect, safety, adherence or in delaying the development of drug resistance in malaria, tuberculosis and HIV/ AIDS."

The modification in 2005 appears to be addressing more than one issue. Given that the agenda for this meeting requires consideration of several applications for new FDCs across three infectious diseases clinical areas, the Secretariat seeks clarification of the principles on which drug selection should be based before consideration of any individual application.

The 2005 modification states that fixed dose combinations need to demonstrate clinical efficacy and safety beyond that for the individual agents given alone. From a regulatory viewpoint, fixed dose combinations would also need to demonstrate bioequivalence of the single combined dose unit with the components administered in the same doses separately but concomitantly. These requirements for efficacy of the combination beyond that of the individual drugs and for bioequivalence are relevant to all clinical areas, including infectious diseases.

The second aspect of the modification relates to adherence. Adherence is important for all clinical areas but of particular and critical importance in the area of infectious diseases, where problems with adherence lead to inadequate and inconsistent dosing and the potential for the development of resistance. FDCs offer the advantage of improved compliance and adherence to therapy and through this mechanism may reduce the development of resistance. Therefore the issue is specifically that of adherence. If adherence were equally good between the single dose unit (FDC) and the same drugs given concomitantly, the impact on resistance would be comparable.
**FDCs and adherence**

There are two recent systematic reviews that address the question of whether FDCs have a positive effect on adherence to medication regimens. These are:


Based on the information in these reviews there are very few clinical trials that assess the relationship between FDCs and adherence to treatment. Connor’s review identified 3 studies that included FDCs specifically; Heneghan et al did not identify any additional trials. The 3 trials in the Connor review all had significant methodological flaws (large losses to follow up; no intention to treat analysis; too short in duration). There is therefore limited direct evidence that strongly supports the benefits of use of FDCs.

Other studies in these two reviews report the impact of co-packaging, or other interventions such as ‘dosette’ boxes or calendar reminders etc. For these interventions, the evidence is more convincing in terms of impact on adherence measured by pill count or self report. Very few studies report outcomes that translate these measures into measures of clinical benefit (e.g. in diabetes, relating adherence to improved glycaemic control). There is some limited evidence from observational and modeling studies that link improvements in adherence to improved clinical outcomes in the cardiovascular area. ³,⁴,⁵

In HIV, there are a number of studies that examine the relationship between pill burden, adherence and development of viral resistance. A review of 22 clinical trials published in 2000 established a relationship between triple therapy, pill burden and viral load, suggesting that higher pill burden was associated with higher viral load after 1 year’s treatment. ⁶ There are some recent observational studies, including Maggiolo et al ⁷, ⁸ and Calmy et al ⁹ that confirm the impact of adherence on virological failure, and the potential benefits of FDCs. Some studies have found no relationship between pill burden and adherence and most now acknowledge that improving adherence requires a multifactorial approach. However, reducing the pill burden appears to be one factor that can be addressed. Improvements in adherence should reduce in part the potential for the development of resistance.

In TB there is ecological evidence of the benefits of FDCs in relation to drug resistance in early studies of DOTS programs. In malaria, combination treatment is now
recommended as standard therapy based on studies showing superior effectiveness of combination treatment compared with monotherapy. The combination therapy reduces the potential for development of resistance, the use of FDCs improves adherence to what are otherwise onerous treatment regimens. Currently, the artemether-lumefantrine tablet combination is the only FDC listed for the treatment of malaria.

The main advantage of FDCs therefore is to improve adherence to therapy. Of themselves FDCs do not reduce the potential for development of resistance beyond that achieved by administering the same drugs separately. An important consideration in the selection of FDCs remains the clinical data - does the combination of drugs (and drug doses) proposed represent the most clinically appropriate choice of drugs (based on comparative efficacy, safety and cost). If this first condition is not satisfied, it is possible that in clinical practice a less optimal FDC is chosen because of its availability and perceived improved adherence rather than its demonstrated clinical benefits.

**WHO review**

A meeting was convened in December 2003 by WHO to discuss the many issues related to Fixed Dose Combination products, ([Fixed-Dose Combinations for HIV/AIDS, Tuberculosis, and Malaria - Report of a Meeting Held 16-18 December 2003 Geneva](http://www.who.int/malaria/docs/TreatmentGuidelines2006.pdf))

The meeting discussed both Fixed Dose Combination products (FDCs) and Co blistered Combinations (CBCs) The main observations of this meeting was that:

- FDCs/CBCs are very important tools for scaling-up treatment for HIV/AIDS, TB and malaria. FDCs remain the first choice when they are available, CBCs are a second choice and single products are a third, but least desirable choice.
- FDCs/CBCs alone are not going to be enough; separate medicines will continue to be needed in specific circumstances, as discussed below. FDCs/CBCs must be considered as one element in an effort to ensure adherence that also includes supportive counselling, appropriate information and other measures.
- FDCs should be based on combinations of clinically proven safety and efficacy, and they must have demonstrated quality and bioequivalence. Where CBCs are used, the requirement is for a logical combination of products of proven safety, efficacy and assured quality.

**Current agenda items**

The current agenda includes several items that are FDCs for infectious diseases: malaria, TB and HIV. All of the proposed products are consistent with WHO current treatment guidelines:

for malaria: [http://www.who.int/malaria/docs/TreatmentGuidelines2006.pdf](http://www.who.int/malaria/docs/TreatmentGuidelines2006.pdf)


for HIV: [http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf](http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf)
In the case of malaria and TB, the guidelines clearly identify preferred combination treatment options, based on clinical studies and reviews that show that combination treatment is superior. The guidelines specify the components needed in each combination and the amount of each. For TB, currently the WHO model list includes all individual medicines and a number of FDCs. For malaria, the proposal is to update the Model List to reflect the current treatment guidelines, and include the preferred FDCs on the Core list where a product exists. This is likely to result in a short list of FDCs.

In the case of HIV, the range of treatment options proposed in the guidelines is substantial and is best summarized in Table 11 from the guidelines reproduced below. There are at least 2 alternatives for each of 3 components for first line treatment options and a larger number of second line alternatives. In addition, there are a number of options proposed as alternatives if toxicity to any one of the individual components develop. All components of these combinations are on the list as individual medicines, or are being considered at this meeting (tenofovir and emtricitabine). Listing only all recommended first line treatment regimens as FDCs would result in listing at least 10 three component FDCs, not all of which yet exist. There are numerous possible two component FDCs as well. Some of these regimens may become more or less preferred as experience with the various combinations accumulate; for example, tenofovir has been registered and available since 2004 only.

A potential risk with listing and availability of only selected HIV FDCs is that management practices in the field may be directed towards less preferred treatment options. A related issue is the pressure for development of FDC products that may be quickly superseded by other drug combinations over time.

Currently available FDCs for HIV, as described in the WHO guidelines are in the second table, reproduced from Annex 10. The guidelines provide some judgments about comparative costs of the FDCs, noting that FDCs containing stavudine have been widely used in ARV rollout because of their relative affordability, whereas FDCs containing abacavir, efavirenz, tenofovir and emtricitabine have either been more costly or not available in resource-poor settings to date. The guidelines also note that FDCs containing stavudine are less preferable now because of the long term toxicity associated with that component.

In summary, it is clear that the preferred FDCs for HIV are still being defined and the science to support the choice is also still evolving. Currently, using the standard selection criteria for an essential medicine it is likely that two triple FDCs (AZT+3TC+nevirapine and D4T+3TC+ nevirapine) might be the preferred options based on comparative effectiveness and cost although the latter is more toxic. Similarly, the preferred double FDCs would probably be AZT+3TC or D4T+3TC, but again with the difference in toxicity. None of these FDCS is currently proposed for addition to the Model List.
Table 11. Detailed recommendations for switching to second-line ARV regimens in adults and adolescents

<table>
<thead>
<tr>
<th>First-line regimen</th>
<th>Second-line regimen</th>
<th>Retin component</th>
<th>Protease inhibitor component a</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard strategy</strong></td>
<td>AZT or d4T + 3TC b + NVP or EFV</td>
<td>ddl + ABC or TDF + ABC or TDF + 3TC (± AZT) c</td>
<td>Pl/r a</td>
</tr>
<tr>
<td></td>
<td>TDF + 3TC b + NVP or EFV</td>
<td>ddl + ABC or ddl + 3TC (± AZT) c</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ABC + 3TC b + NVP or EFV</td>
<td>ddl + 3TC (± AZT) c or TDF + 3TC (± AZT) c</td>
<td></td>
</tr>
<tr>
<td><strong>Alternative strategy</strong></td>
<td>AZT or d4T + 3TC b + TDF or ABC</td>
<td>EFV or NVP ± ddl</td>
<td></td>
</tr>
</tbody>
</table>

a. NFV does not need refrigeration and can be used as a PI alternative in places without a cold chain.
b. 3TC and FTC are considered interchangeable because they are structurally related and share pharmacological properties and resistance profiles.
c. 3TC can be considered to be maintained in second-line regimens to potentially reduce viral fitness, confer residual antiviral activity and maintain pressure on the M184V mutation to improve viral sensitivity to AZT or TDF. AZT may prevent or delay the emergence of the K65R mutation.
d. There are insufficient data to detect differences among currently available RTV-boosted PIs (ATV/r; FFV/r; IDV/r; LPV/r and SQV/r) and the choice should be based on individual programme priorities (see text). In the absence of a cold chain, NFV can be employed as the PI component but it is considered less potent than an RTV-boosted PI.

<table>
<thead>
<tr>
<th>Three-drug fixed-dose combinations</th>
<th>AZT + 3TC + ABC (co-formulation and co-blistier)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AZT + 3TC + NVP (co-formulation and co-blistier)</td>
</tr>
<tr>
<td></td>
<td>AZT + 3TC + EFV (co-blistier)</td>
</tr>
<tr>
<td></td>
<td>d4T + 3TC + NVP (co-formulation)</td>
</tr>
<tr>
<td></td>
<td>TDF + FTC + EFV (co-formulation)</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Two-drug fixed-dose combinations</th>
<th>ABC + 3TC (co-formulation)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>AZT + 3TC (co-formulation)</td>
</tr>
<tr>
<td></td>
<td>d4T + 3TC (co-formulation)</td>
</tr>
<tr>
<td></td>
<td>LPV/r (co-formulation)</td>
</tr>
<tr>
<td></td>
<td>TDF + FTC (co-formulation)</td>
</tr>
</tbody>
</table>

a. Co-formulations are based on the principle of inclusion of two or more active pharmacological products in the same capsule, tablet or solution.
b. Blister packs is defined a plastic or aluminium blister containing two or more capsules or tablets.
**Proposed action**

The Committee is requested to review its current criteria for listing FDCs and if necessary, modify the text in the 'Procedures'.

It would seem appropriate to list FDCs when a disease program has direct clinical evidence of the efficacy, safety and cost-effectiveness of preferred combination treatments and there are products of satisfactory quality available that satisfy the specification. Where there are multiple FDCs for a particular indication, it is suggested that the usual criteria for selecting essential medicines apply (comparative effectiveness, safety and cost).

Where there is insufficient clinical evidence to support particular drug combinations, the individual components may be listed if appropriate. If a product is co-packaged but not formulated as an FDC, this can be assumed to be covered by listing individual components.

**References**


8. Maggiolo F et al. **Similar Adherence Rates Favor Different Virologic Outcomes for Patients Treated with Nonnucleoside Analogues or Protease Inhibitors.** *Clinical Infectious Diseases* 2005; 40:158–163.