WHO MODEL LIST OF ESSENTIAL MEDICINES APPLICATION

zidovudine/lamivudine fixed-dose combination tablets for the treatment of HIV-1 infection

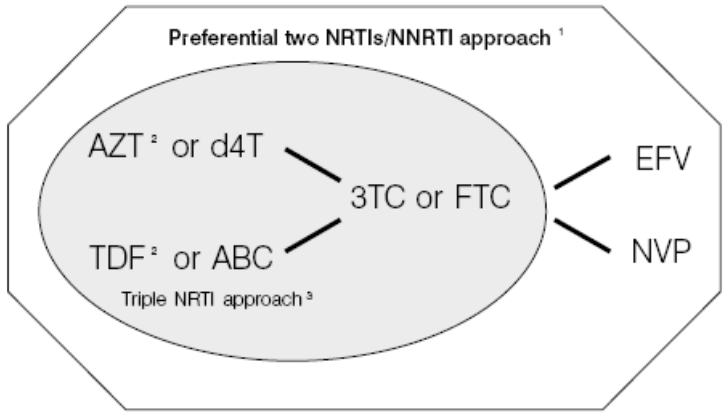
1. Summary statement of proposal for inclusion, change, or deletion

The combination tablet of zidovudine/lamivudine (AZT/3TC) is proposed for inclusion on the WHO Model List of essential medicines for the treatment of HIV infection. The fixed dose combination (FDC) of AZT/3TC was last considered by the Expert Committee in 2002 but a decision was made to only list individual anti-retroviral drugs at that time. Because of the importance of FDCs on WHO plan towards to universal access to ART until 2010 and the growing number of products that have been assessed for quality and approved by WHO and other regulatory authorities it was felt appropriate to reconsider the listing of this product. A detailed review of the evidence on efficacy and safety was compiled by the Cochrane HIV/AIDS group for the Expert Committee in 2002 and that submission is provided to the Committee for reference. This submission will include a briefer updated summary of data on efficacy and safety.

The principal reasons for requesting this inclusion are as follows:

1. Modern anti-retroviral therapy (ART) mandates the use of three or more drugs and this can require a large number of tablets to be swallowed each day and used lifelong.
2. The efficacy of current ART can be compromised with quite small reductions in adherence.
3. Fixed dose combinations of appropriate antiretroviral drugs improve adherence and efficacy and may reduce the development of viral resistance
4. The WHO guidelines for Antiretroviral Therapy for HIV Infection in Adults and Adolescents 2006 (WHO Guidelines) emphasise the need for a public health approach with simplification of treatment regimens, particularly the use of fixed dose drug combinations that enable once or twice daily dosing and also facilitates the programmatic and logistics aspects. The Guidelines also emphasise the selection of suitable combinations and consideration of price and cost-effectiveness.
5. The WHO Guidelines recommend first line therapy with a dual nucleoside reverse transcriptase inhibitor (NRTI) and a non-nucleoside reverse transcriptase (NNRTI). The combination of AZT and 3TC represents a popular dual NRTI backbone, which can be combined with a NNRTI another NRTI or a protease inhibitor.
6. The WHO Guidelines lay out a number of desirable combination therapies, which include AZT/3TC. The attractions of this combination are its efficacy (as reviewed in this submission), tolerability, wide availability from multiple suppliers, relatively low cost, wide practical experience and safety data in a range of settings. Other possible NRTI combinations comprising tenofovir (TDF) and emtricitabine (FTC) or lamivudine (3TC) are also appropriate. Experience with them in low and middle income countries is more limited; they have fewer suppliers and are higher priced.

Fig. 1. First-line ARV drugs for adults and adolescents



1 Preferential two NRTIs/NNRTI approach is based upon a combination of three drugs: two NRTIs combined with either NVP or EFV as the NNRTI.
2 Preferred NRTI to be combined with 3TC or FTC in standard first-line regimens.
3 Triple NRTI approach (i.e. three NRTI drugs selected only from the options shown within the dotted circle) can be considered as an alternative for first-line regimens in situations where NNRTI options provide additional complications (e.g. women who have CD4 counts between 250 and 350 cells/mm³, viral hepatitis coinfection, TB coinfection, severe reactions to NVP or EFV, and HIV-2 infection) as discussed above.

Note AZT = zidovudine, d4T = stavudine, 3TC = lamivudine, TDF = tenofovir, FTC = emtricitabine, ABC = abacivir, EFV = Efavirenz, NVP= nevirapi

2. Name of focal point in WHO supporting the application

Charles Gilks Coordinator Anti-retroviral Treatment and HIV Care (ATC)

3. Name of the organisation(s) consulted and/or supporting the application

4. International Nonproprietary Name (INN)

zidovudine/lamivudine

5. Formulation proposed for inclusion

Combination tablet comprised of zidovudine 300mg and lamivudine 150mg.

6. International availability

Section 13 (see Table 13.1) provides a list of the manufacturers. Three manufacturers, Aurobindo Pharma Ltd (India), Aspen Pharmacare (South Africa) and Apotex Inc (Canada) supply fixed-dose combination tablets that have WHO prequalification status.

7. Category of listing requested

Listing is requested as fixed dose combination of the antiretrovirals group, including two nucleoside reverse transcriptase inhibitors (zidovudine and lamivudine).

8. Information supporting the public health relevance

8.1 Epidemiological information on disease burden

Current estimates indicate that 39.5 million people were living with HIV in 2006, with a total of 4.3 million new infections in 2006[1]. Developing

countries, in particular sub-Saharan African countries, are the most affected countries in the world, with 24.7 million people with HIV (63%)[1]. The majority of AIDS-related deaths occur in sub-Saharan Africa (2.1 million of the 2.9 million deaths globally)[1].

Of the 4.3 million new infections, 2.8 million (65%) occurred in sub-Saharan Africa, 860,000 (31%) in South Asia and 270,000 (9%) in Eastern Europe and Central Asia[1].

Table 8.1.1 summarises the number of people living with HIV, the number of AIDS deaths and the number of new infections world-wide in 2006.

Table 8.1.1: Summary of HIV infection, new cases and AIDS deaths in 2006

Region	People living with HIV 2006	New infections 2006	AIDS deaths 2006
Sub-Saharan Africa	24,700,000	2,800,000	2,100,000
South and Southeast Asia	7,800,000	860,000	590,000
East Asia	750,000	100,000	43,000
Latin America	1,700,00	140,000	65,000
North America	1,400,000	43,000	18,000
Western and Central Europe	740,000	22,000	12,000
Eastern Europe and Central Asia	1,700,000	270,000	84,000
Middle-east and North Africa	460,000	68,000	36,000
Caribbean	250,000	27,000	19,000
Oceania	81,000	7,100	4,000
Total	**39,500,000**	**4,300,000**	**2,900,000**

Source: http://www.who.int/hiv/mediacentre/20061121_EPI_FS_GlobalFacts_en.pdf

Table 8.1.2 provides the number of people receiving antiretroviral (ART) therapy in developing countries.

Table 8.1.2: Summary of ARV treatment

Region	Number receiving ARV therapy June 2006	Number requiring therapy 2005	ARV therapy coverage June 2006
Sub-Saharan Africa	1,040,000	4,600,000	23%
Latin America and Caribbean	345,000	460,000	75%
East, South and Southeast Asia	235,000	1,440,000	15%
Eastern Europe and Central Asia	24,000	190,000	13%
Middle-east and North Africa	4,000	75,000	5%
Total	**1,650,000**	**6,800,000**	**24%**

Source: http://www.who.int/hiv/mediacentre/20061121_EPI_FS_GlobalFacts_en.pdf

Although the number of people receiving ARV therapy in developing countries has increased to 24% of those requiring therapy from 7% in December 2003, the proportion treated in these countries remains low[1].

It is recognised that highly active antiretroviral (HAART) therapy has resulted in a decline in mortality in both the developed and developing world[2]. The WHO "Antiretroviral Therapy for HIV Infection in Adults and Adolescents" Guidelines (2006 revision) recommend a combination of two NRTI and one NNRTI as the preferred first-line option in developing countries [3]. Given that successful therapy requires high levels of adherence[8], fixed dose combinations, which eliminate high pill burden associated with combination therapy, assist in achieving successful therapy. The WHO Model List of Essential Medicines states that "In order to simplify treatment, facilitate storage and distribution, and improve patients' adherence to the treatment plan, the Committee recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations" (WHO Model List 14th edition March 2005, 6.4.2 Antiretrovirals).

Thus, inclusion of the fixed dose combination of AZT/3TC on the WHO Model List is sought. Evidence demonstrating the efficacy and safety of AZT/3TC/ is provided in Section 10.2 and Section 11 of this submission and in the submission made to the Expert Committee in 2002.

8.2 Assessment of current use

The current WHO Guidelines (2006 revision) state that the preferred NRTI backbone is composed of zidovudine or tenofovir combined with either lamivudine or emtricitabine, with either nevirapine or efavirenz added. It is difficult to obtain drug consumption data but AZT/3TC is a popular dual NRTI backbone, which when combined with NNRTIs has become a standard treatment and international experience with its use is widespread.

8.3 Target population

Patients with HIV infection who qualify for treatment with ARV therapy. According to the WHO Guidelines this is usually defined as presence of advanced/severe symptomatic disease or asymptomatic individuals with a CD4 count of 200 cells/mm^2 or less, although a higher threshold level can be used in the presence of mild clinical illness (see WHO Guidelines).

9. Treatment details

9.1 Dosage regimen

The recommended dose of the combination tablet is one tablet taken twice daily giving a total daily dose of 600 mg zidovudine and 300mg lamivudine. Modern treatment guidelines require that dual NRTI treatment is not used alone and the FDC has to be co-prescribed with a NNRTI another NRTI or with a protease inhibitor.

9.2 Treatment duration

Treatment duration is life-long – or until treatment has to be ceased, modified or switched because of adverse effects, contraindications or therapeutic failure.

9.3 Reference to WHO and other clinical guidelines

The WHO "Antiretroviral Therapy for HIV Infection in Adults and Adolescents" Guidelines (2006 revision)[3] state that the preferred NRTI backbone is composed of zidovudine or tenofovir combined with either lamivudine or emtricitabine, with either nevirapine or efavirenz added.

The 2006 US Department of Health and Human Services (DHHS) Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents[8] recommendation is for the use of co-formulated zidovudine/lamivudine combined with either efavirenz (preferred) or nevirapine (alternative).

9.4 Need for special diagnostic or treatment facilities and skills

The WHO Guidelines (2006) recommend that facilities be available to perform the following tests: confirmation of HIV infection status; measurement of CD4 (where possible); hemoglobin measurement if initiation of AZT is being considered; pregnancy test in women if initiation of efavirenz is being considered; screening for TB and malaria, and diagnostic testing for other co-infections and opportunistic diseases where clinically indicated.

10. Summary of comparative effectiveness

Note: in compiling this application, it was recognised that there are large numbers of commercial products available around the world; some have been subject to rigorous regulatory assessment while others have not. Few have been tested in large scale clinical endpoint trials. It is therefore not possible to find a data-set that represents the real world efficacy of all the FDCs containing the component drugs. So the application proposes that that adequately conducted trials of either a FDC, or trials involving concomitant administration of the component drugs, provide evidence of the *potential* efficacy of the FDCs. In other words these studies are indicative not conclusive. But also it is also assumed that, if the FDC products have been approved after a suitable rigorous evaluation (e.g. WHO, FDA, EMEA), which involves assessment of bioavailability, the trial efficacy data can be applied to them.

10.1 Identification of clinical evidence

10.1.1 Search strategy

Medline, Embase and the Cochrane Library were searched for relevant trials comparing dual drug (AZT/3TC) with three or four drug antiretroviral maintenance regimens for HIV infection. The search terms used were:

1. zidovudine
2. lamivudine
3. 1 and 2
4. 3 and generic
5. 3 and toxicity

6. 3 and adverse events
7. 3 and randomised controlled trial
8. 3 and systematic review
9. 3 and Fixed Dose Study.

10.1.2 Systematic reviews identified:

Two systematic reviews were identified that examined AZT/3TC versus mono, triple or four drug therapy for HIV infection.

One Cochrane Review (Rutherford et al 2003)[2] was identified, which compared the use of three- or four- versus two-drug antiretroviral maintenance regimens following successful initial three or four-drug retroviral therapy for HIV infection. Specifically, two trials and one abstract compared AZT/3TC to other dual and triple combination therapies.

A second systematic review by Jordan et al (2002)[3] was identified, which assessed the evidence for the effectiveness of increasing numbers of drugs in antiretroviral combination therapy. Four trials compared AZT/3TC to monotherapy and two trials compared AZT/3TC to triple therapy.

As mentioned earlier the 2002 submission to the Expert Committee included a summary of efficacy and safety data compiled by the Cochrane Review Group for HIV/AIDs. That document is also provided as background.

Given that AZT/3TC is already a well established NRTI backbone to which a NNRTI or protease inhibitor is normally added, this application will summarise only the two systematic reviews referred to above.

10.1.3 Selection/exclusion of particular data

The Cochrane Review (Rutherford et al 2007) selected randomised controlled trials in which HIV-infected adults had successfully completed initial three or four–drug antiretroviral therapy and who were randomised to receive maintenance therapy with three or four drugs or maintenance therapy with two drugs. Successful initial therapy was defined by a plasma viral load of less than 500 copies/ml.

The systematic review by Jordan et al (2002)[3] selected randomised controlled trials of antiretroviral therapy in HIV positive patients ≥ 12 years with less than 6 months previous antiretroviral therapy. Studies were excluded if they lasted less than 12 weeks.

Selected trials from the reviews are summarised in Table 10.1.3.1:

Table 10.1.3.1: Selected data

Trial	Design
Randomised comparative trials Cochrane Review (Rutherford et al, 2007)[2].	
Havlir, 1998	• Randomised, double blind trial, comparing AZT/3TC to triple combination therapy Indinavir, lamivudine and stavudine (continued induction therapy). • trial duration 24 weeks.
Flandre, 2002	• Randomised, open-label trial comparing AZT/3TC to Indinavir, lamivudine and zidovudine (continued induction therapy). •trial duration 2 months
Clumek, 1999	• Random allocation, open label trial, comparing AZT/3TC to two nucleoside reverse transcriptase inhibitors plus indinavir or ritonovir plus saquinivir (continued induction therapy). •trial duration 12 weeks.
Randomised comparative trials Systematic Review (Jordan et al, 2002)[3].	
Eron et al, 1995	•Randomised controlled trial comparing AZT/3TC versus either AZT alone or 3TC alone. • trial duration > 12 weeks.
Katlama et al, 1996	•Randomised controlled trial comparing AZT/3TC versus AZT • trial duration > 12 weeks.
Kuritzkes et al, 1999	• Randomised controlled trial comparing AZT/3TC versus stavudine. • trial duration > 12 weeks.
Quattro Steering Committee (1999)	• Randomised Controlled trial comparing AZT/3TC versus ZDV-Lam-Lov-Zalc. • trial duration > 12 weeks.
Gatell et al, 1999	• Randomised controlled trial to compare AZT/3TC versus AZT/3TC + lovride. • trial duration > 12 weeks.
Conway, B (2000).	• Randomised Controlled trial comparing AZT/3TC versus AZT/3TC + delavirdine. • trial duration > 12 weeks.

10.2 Summary of available data

10.2.1 Appraisal of quality

All studies included in the Cochrane Review had objective baseline measurements and objective and reliable outcome measures.

The trial by Havlir et al (1998) used centralised randomisation and appropriate concealment of allocation. All 309 participants were followed to the end of the trial. ITT approach was used in all cases.

The trial by Flandre 2002 did not explain how allocation was concealed. The study was open label and all 297 randomised participants were followed to the completion of the trial. All analyses was conducted on an ITT basis.

No randomisation scheme is described by Clumek, 1999. The trial is open label and uses ITT analysis.

The systematic review by Jordan et al (2002) described the included trials as randomised good quality trials. Concealment of allocation was confirmed in

a third, most were double blind and participants in each arm were comparable within trials. The length of the trials varied from 12 weeks to 4.8 years, although follow-up was not clearly reported.

10.2.2 Outcome measures

The main outcome measure in the Cochrane Review was plasma HIV viral load.

The main outcome measures in the 2002 systematic review (Jordan et al, 2002)[3] were; changes in disease progression or death (clinical outcomes): CD4 count and plasma viral load (surrogate markers).

10.2.3 Summary of results – Cochrane Review.

The following table lists the baseline characteristics of the three relevant trials from the Cochrane Review.

It should be noted that, in common with other submissions, it is often not clear whether the trials employed a fixed dose combination or concomitant therapy with the individual component drugs. As we have relied on secondary data sources in compiling this submission we have not attempted to distinguish the products that were used.

Table: 10.2.3.1: Characteristics of participants in selected randomised trials from the Cochrane Review[2].

Havlir Study	
Participants	343 HIV-infected adults with no prior PI therapy and with >200 CD4+ cells/ml and >1000 plasma HIV RNA copies/ml who had successfully undergone six months of induction therapy with indinavir, lamivudine and stavudine (<200 plasma HIV RNA copies/ml at 16, 20 and 24 weeks)
Flandre Study	
Participants	279 HIV-infected, antiretroviral naive adults with >600 CD4+ cells/ml and 3,500-100,000 plasma HIV RNA copies/ml who had successfully undergone three months of induction therapy with indinavir, lamivudine and zidovudine (<500 plasma HIV RNA copies/ml at two months)
Clumik Study	
Participants	40 HIV-infected adults with no prior PI treatment and with >100 CD4+ cells/ml and >5000 plasma HIV RNA copies/ml who had successfully undergone four months of induction therapy with two nucleoside reverse transcriptase inhibitors plus either indinavir or ritonovir plus saquinivir (<400 plasma HIV RNA copies/ml at 12 weeks)

Results from the Cochrane Review:

Table: 10.2.3.2: Overall Results from the Cochrane Review (Rutherford et al: 2007)[2].

Study	Loss of viral suppression (AZT/3TC)	Loss of viral suppression (3 or 4 drug therapy)	Odds Ratio	95% CI
Combining all four studies in the Cochrane Review*	116/324	19/235	5.55	3.14-9.80
Combining Havlir/Flandre trials	51/198	14/2197	4.58	2.43-8.64
Discontinuation of one or more PIs after after inclusion in the induction therapy*	84/222	19/235	7.92	4.5-13.95.

Abbreviations: PIs = Protease Inhibitors.
* Only 3 trials out of the four were relevant to this application; however results were only provided combining all four trials in these cases and individual trial results were not described.

Overall loss of viral suppression (loss of efficacy) was substantially greater for those on the dual combination maintenance therapies (AZT/3TC) compared to those who continued prolonged induction on three or four drug maintenance therapies.

10.2.4 Summary of Results – Systematic Review (Jordan et al, 2002)[3].

10.2.4.1 Characteristics of participants in this review:

Over 80% of the participants in this review were men with an average age ranging from 27 and 40 years. Mean baseline CD4 counts ranged from 83-660 cells per ul and mean viral load ranged from 2.35 to 7.35 log copies per ml.
The following tables describe the main results from the Systematic Review (Jordan et al, 2002)[3]:

Table 10.2.4.2 The effect of double therapy versus monotherapy or triple therapy on disease progression or death (Jordan et al, 2002)[3].

Double therapy versus monotherapy			
Study	**Double therapy (AZT/3TC) Number of events/ Number of participants**	**Monotherapy Number of events/ Number of participants**	**Odds ratio (95% CI) (Results <1 favoured double therapy)**
Eron et al, 1995	0/92	3/93	0.13 (0.01 -1.30)
Katlama et al, 1996	1/65	0/64	7.28 (0.14-366.77)
Kuritzkes et al, 1999	NR	NR	NR
Quattro 1999	5/32	7/34	0.72 (0.21-2.49)
Triple therapy versus double therapy			
Study	**Double therapy (AZT/3TC) Number of events/ Number of participants**	**Triple therapy Number of events/ Number of participants**	**(Results <1 favour triple therapy).**
Gatell et al, 1999	2/52	2/54	0.96 (0.13-7.03)
Conway	NR	NR	NR

Abbreviations: NR= Not reported. Source: Source: figures 6 and 9, (Jordan et al, 2002).

Overall, double therapy resulted in significantly better outcomes than monotherapy did. The exception is the small Katlama trial (1996), which had a trend in favour of monotherapy. The Gatell trial slightly favours triple therapy over double therapy, although outcomes are rare in this and the other studies.

Table 10.2.4.2 The effect of double therapy versus monotherapy or triple therapy on change in mean (SD) CD4 count (cells per uL) (Jordan et al, 2002).

Double therapy versus monotherapy			
Study	**Double therapy (AZT/3TC) Number of participants/ mean (SD)**	**Monotherapy Number of participants/ mean (SD)**	**Weighted Mean Difference (95% CI) (>0 favours double therapy)**
Eron et al, 1995	24/ 32(123)	28 /-17(119)	49 (-17.06-115.06)
Katlama et al, 1996	27/40 (153)	28/-17(119)	57(-15.62-129.62)
Kuritzkes et al, 1999	49/ 84.4 (127.4)	16/ 48.1(115.8)	NR
Quattro 1999	29/40 (115)	30/18(118.8)	22 (-37.76-81.76)

Triple therapy versus double therapy			
Study	**Double therapy (AZT/3TC) (n)of participants/ mean (SD)**	**Triple therapy (n)of participants/ mean (SD)**	**Weighted Mean Difference (95% CI) (>0 favour triple therapy)**
Gatell et al, 1999	NR	NR	NR
Conway	NR	NR	NR
Total*	510	735	40.8 (25.1- 56.4)

Abbreviations: NR= Not reported. Source; Figures 7 and 10 (Jordan et al, 2002).
***= data from all trials in the review comparing double and triple therapy only.**

Results for CD4 counts tended to favour double therapy over monotherapy.

Table 10.2.4.3 The effect of double therapy versus monotherapy or triple therapy on change in mean (SD) viral load(log copies per mL) (Jordan et al, 2002)[3].

Double therapy versus monotherapy			
Study	**Double therapy (AZT/3TC) (n)of participants/ mean (SD)**	**Monotherapy (n)of participants/ mean (SD)**	**Weighted Mean Difference (95% CI) (<0 favours double therapy)**
Eron et al, 1995	33/-0.99 (0.73)	31/-0.25 (0.47)	-0.74 (-1.039-0.441)
Katlama et al, 1996	25/-1.20 (0.59)	23 /-0.30 (0.51)	-0.90(-1.211- -0.589).
Kuritzkes et al, 1999	45/ -0.84(0.79)	16/-0.41(0.62)	-0.430 (-0.812- -0.048)
Quattro 1999	28 /-0.78 (0.55)	27/-0.73(0.92)	-0.050(-0.452-0.l352)
Triple therapy versus double therapy			
Study	**Double therapy (AZT/3TC) (n)of participants/ mean (SD)**	**Triple therapy (n)of participants/ mean (SD)**	**Weighted Mean Difference (95% CI) (<0 favours triple therapy).**
Gatell et al, 1999	NR	NR	NR
Conway	NR	NR	NR
Total*	246	408	-0.542 9-0.679- -0.404).

Abbreviations: NR= Not reported. Source; Figures 8 and 11 (Jordan et al, 2002).
***= data from all trials in the review comparing double and triple therapy only**

Double therapy resulted in significantly better clinical outcomes than monotherapy (The total odds ratio for disease progression/death was 0.6; 95% CI 0.5 to 0.7). Results for changes in surrogate markers were significantly better with double therapy than with monotherapy.

Triple therapy significantly improved clinical outcomes compared with double therapy. (overall odds ratio for disease progression/death was 0.6, 0.5-0.8). The results for CD4 and viral load were consistent with those for the clinical outcomes showing that triple therapy was significantly better than double therapy (although the trials that were selected from this systematic review for this application had limited data).

10.3 Summary of available estimates of comparative effectiveness

Overall, results show that combinations with two or more drugs were significantly more effective than monotherapy. In turn, combinations of three or more drugs were significantly more effective than dual therapy. The results show unambiguous evidence of the efficacy of AZT/3TC but also show that the two-drug FDC should not be used on its own, and has to be combined with another NRTI, a NNRTI or protease inhibitor to achieve an acceptable degree of efficacy.

10.4 Adherence to Fixed Dose Combinations

Research has suggested that the more complicated the treatment regimen, the more likely it is for one or more doses to be missed (Mehta et al, 1997)[4]. Forgetfulness is a major cause of missed doses, a problem that could be potentially exacerbated in patients whose memory is affected by AIDS-relative cognitive disorder (Corless et al, 2000)[5].

A cohort study that compared AZT and 3TC as fixed dose combinations versus each component taken as separate pills was used to examine the association between treatment group and medication adherence[6]. The likelihood of ≥ 95% adherence among patients on the fixed dose combination therapy was three times greater than patients taking 3TC and AZT as separate pills. In addition, combination therapy patients had on average 1.4 fewer adherence failures per year of follow-up and nearly double the time to adherence failure compared to the separate pills groups[6].

A randomised, open label, multicentre study by Eron et al (2000)[7] studied the adherence with a twice daily combination of 3TC/AZT tablet formulation, plus a protease inhibitor versus AZT and 3TC as separate pills with a protease inhibitor. A self reported adherence

questionnaire indicated that patients in the combination tablet group were less likely to miss doses of nucleoside analogue medication at weeks 8 (P=0.007) and 16 weeks (P=0.046) (Eron et al, 2000)[7].

11. Summary of comparative evidence on safety

11.1 Estimate of total patient exposure to date

Data are not available but this is a popular combination product that has a large number of manufacturers and is widely recommended in many guidelines. As an increasing number of triple FDCs have become available they will tend to reduce the use of the dual combination products. An exception is where a 'lead in' dose approach is thought necessary. For instance patients may be advised to take AZT/3TC in the morning and AZT/3TC/NVP in the evening for the first 14 days of treatment to reduce the initial toxicity experienced with NVP. After the initial lead in phase the patient takes AZT/3TC/NVP twice daily.

11.2 Description of adverse effects/reactions

Drug intolerance and elevated levels of viral load caused only 64% (663) of the original 1034 patients who entered the trials presented in the Cochrane Review to be randomised. Of the 663 patients who made it to maintenance phase, 152 did not achieve sufficient viral suppression and 67 withdrew because of drug intolerance during initial treatment. No specific adverse effects were described in the Cochrane Review.

No specific adverse reactions were described in the systematic review by Jordan et al (2002)[3]. However, drop out rates were described as no different between double therapy (AZT/3TC) and monotherapy. The results of the triple therapy versus double therapy were heterogeneous. Subgroup classification of trials according to the presence of protease inhibitors suggested that there was no significant difference in drop out rates between triple therapy without a protease inhibitor and double therapy without a protease inhibitor. Trials that contained a protease inhibitor in the triple but not the double arm had significantly higher withdrawal rates.

Adverse effects/reactions: headache, malaise and fatigue, nasal signs and symptoms, cough, diarrhoea, nausea and vomiting, neuropathy, musculoskeletal pain, insomnia and other sleep disorders, dizziness, fever or chills, abdominal pain, depressive disorders, skin rashes, myalgia, abdominal cramps, arthralgia, dyspepsia.

Laboratory abnormalities (Grade 3 or 4): neutropenia, anemia, thrombocytopenia; elevated amylase, ALT, AST, bilirubin.

Warnings:
Combinations of lamivudine + zidovudine should be used with caution in patients who have bone marrow compromise evidenced by granulocyte count <1,000 cells/mm^3 or haemoglobin <9.5 g/dL. Frequent blood counts

are strongly recommended in patients with advanced HIV disease who are treated with fixed-dose lamivudine + zidovudine. For HIV-infected individuals and patients with asymptomatic or early HIV disease, periodic blood counts are recommended. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including lamivudine, zidovudine and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged exposure to antiretroviral nucleoside analogues may be risk factors. Particular caution should be exercised when administering zidovudine to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with zidovudine should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations). Myopathy and myositis, with pathological changes similar to that produced by HIV disease, have been associated with prolonged use of zidovudine, and therefore may occur with therapy with fixed-dose lamivudine + zidovudine. Changes in skin and nail pigmentation have been reported with the use of zidovudine.

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown.

11.3 Identification of variation in safety due to health systems and patient factors

None.

11.4 Summary of comparative safety against comparators

Overall, a greater occurrence of adverse events was observed in triple combination therapy versus double therapy. Significantly more drop out rates were observed with triple combination therapies that contained a protease inhibitor compared to AZT/3TC alone (Jordan et al, 2002)[3].

12. Summary of available data on comparative cost and cost-effectiveness

12.1 Range of costs of the proposed medicine

Based on the Global Price Reporting Mechanism (http://www.who.int/hiv/amds/gprm/en/) the unit price of ATZ/3TC ranges from $0.01 (Armenia) to $4.99 (Bulgaria), with the average cost of treatment ranging from $8 to $3543 per patient per year. The weighted average price of AZT/3TC in 2005 in low income countries was $USD208 per patient per year (http://who.int/enitity/hiv/AMDS/PriceARV2005.pdf)

12.2 Comparative cost-effectiveness (presented as range of cost per routine outcome)

There have been a number of attempts to quantify the cost-effectiveness of anti-retroviral therapy in low and middle income countries. Some of these have attempted to contrast ARV treatment with preventive measures. The systematic review published by Creese et al., using costs for the year 2000, estimated that the cost per life year or disability adjusted life year gained by HAART lay between $US 1100 and 1800.[8] Any value like this will be sensitive to the costs that were included in the model and the prices paid for ARV therapy. A judgement about cost-effectiveness is very context specific and will depend heavily on the perspective of the payer. A more recent study from the University of Capetown in South Africa (Cleary et al 2004. http://www.hst.org.za/uploads/files/arv_cost.pdf)[9] used a Markov model to simulate the outcomes and costs of introducing ARV therapy into a South African township. The study included a wide range of direct costs, but no productivity gains resulting from effective treatment. The treatment scenarios used in this study included use of the GlaxoSmithKline brand of AZT/3TC at an annual cost (excluding markup) of R1980 (equivalent to around $US250). The model used by the investigators also included the use of branded non-nucleoside transferase inhibitors nevirapine and Efavirenz, and other second line drugs, which are more expensive. The average annual purchase cost of the ARV combinations used in the analysis was 4000 to 5000 Rand ($US 550 – 700), which is substantially higher than what can be achieved in some international markets. Nevertheless, the overall cost-effectiveness of treatment was estimated to be 13620 Rands per QALY gained, approximately $US 1900/QALY. In a country with a per capita GNI of $US 4960 in 2005 (http://siteresources.worldbank.org/DATASTATISTICS/Resources/GNIPC.pdf) this might be considered cost-effective. In lower income countries, where direct costs other than drugs may be lower, and where use is made of lower priced regimens the cost/QALY gained would be less, particularly if productivity gains were included.

13. Regulatory status

Table 13.1 provides the regulatory status of AZT/3TC as recorded in the WHO drugs database (2007)[10]. The majority of the information on the regulatory status of the drugs in the WHO database has been provided by the manufacturers only. Countries in which AZT/3TC has been registered and the information confirmed by the national drug regulatory authority includes India, the USA and South Africa. Three manufacturers, Aurobindo Pharma Ltd (India), Aspen Pharmacare (South Africa) and Apotex Inc (Canada) supply fixed-dose combination tablets which have WHO prequalification status. The original branded product Combivir (GSK) has been approved by most major regulatory agencies around the world.

Table 13.1 – Regulatory status as based on WHO drugs database

INN and dosage	Manufacturer and country	Countries that have granted registration
Lamivudine 150mg + zidovudine 300mg	*Cipla Ltd, India	Benin, Gambia, Mauritania, Nigeria, Sierra, Leone, Uganda, Zambia.
	*Aurobindo Pharma Ltd, India,	Burkino Faso, Ethiopia, Nigeria, Kenya, USA, United Republic of Tanzania, Zambia.
	*GSK Ltd, UK	Azerbaijan, Bahamas, Bangladesh, Barbados, Belize, Bhutan, Cambodia, Cape Verde, Comoros, Korea, Timor-Leste, Equatorial Guinea, Entrea, Georgia, Ghana, Guinea-Bissau, Guyana, Kiribati, Kyrgyzstan, Lao Peoples Democratic Republic, Liberia, Madagasgar, Maldives, Mongolia, Nepal, Pakistan, Papa New Guinea, Sao Tome and Principe, Sierre Leone, Solomon Islands, Syrian Arabian Republic, Turkmenistan, Tuvalu, Vanuata, Yemen.
	*Ranbaxy Ltd, India	India. Ecuador, Kenya, Malawi, Myanmar, Nigeria, Peru, South Africa, Trinidad and Tobago, Uganda, Zimbabwe.
	*Hetero Drugs, India	Burundi, Congo, Gambia, Myanmer, Cote d' Ivoire.
	*Strides Arcolab Ltd, India,	Peru.
	Apotex Inc, Canada[a]	WHO prequalified

[a] this was not included in the WHO drugs database, which was last updated in October 2005

* All are currently WHO pre-qualified.

Source: http://www.who.int/hiv/amds/patents_registration/drs/ . Updated Feb, 2007.

14. Availability of pharmacopoeial standards

Pharmacopoeial standards for the individual components have been promulgated widely internationally. A search for pharmacopoeial standards for the fixed dose combination of AZT and 3TC was not successful.

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