WHO MODEL LIST OF ESSENTIAL MEDICINES APPLICATION

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

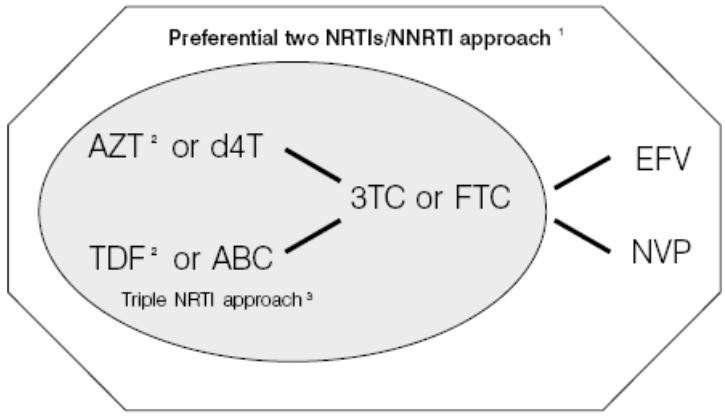
1. Summary statement of proposal for inclusion, change, or deletion

The combination tablet of zidovudine/lamivudine/nevirapine (AZT/3TC/NVP) is proposed for inclusion on the WHO Model List of Essential Medicines for the treatment of HIV infection. 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 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 & 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 a dual NRTI backbone with a protease inhibitor is recommended as second line therapy. The reasons given for this choice include the following statement “regimens based on combination of two NRTIs plus one NNRTI are efficacious, are generally less expensive than other regimens, have generic formulations, are often available as FDCs and do not require a cold chain. In addition, they preserve a potent new class (protease inhibitors) for second-line treatments.”
6. The WHO Guidelines lay out a number of desirable combination therapies, which include AZT/3TC/NVP. The attractions of this combination are its efficacy (as reviewed in this submission), tolerability, wide availability from multiple suppliers and 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.

WHO Guidelines: Figure outlining first line regimens:

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= nevirapine

2. Name of focal point in WHO submitting the application
Charles Gilks

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

4. International Nonproprietary Name (INN)

zidovudine/lamivudine/nevirapine

5. Formulation proposed for inclusion

Combination tablet comprised of zidovudine 300mg, lamivudine 150mg and nevirapine 200mg.

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 which 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) and one non-nucleoside reverse transcriptase inhibitor (nevirapine).

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**

1. 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 options in developing countries[3]. Given that successful therapy requires high levels of adherence[4]), 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/NVP on the WHO Model List is sought. Evidence demonstrating the efficacy and safety of AZT/3TC/NVP is provided in Section 10.2 and Section 11.

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 of the non-nucleoside drugs nevirapine or efavirenz. AZT/3TC/NVP is a long-established FDC and is likely to be widely used. In the case of d4T/3TC/NVP there are published observational studies documenting its widespread use in resource poor settings. As noted below this was not the case with AZT/3TC/NVP, where we have not found reports of large observational studies conducted in low and middle income countries. There are a number of cohort studies describing the use of combination drugs in developed countries and given the wide availability, broad acceptability and price of AZT/3TC/NVP its use is clearly widespread. However we have not been able to identify a source of international data on drug consumption.

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 the 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. The combination tablet should not be administered to patients who have just initiated therapy with nevirapine. This is because an initial lead-in dosing of 200 mg nevirapine once daily for 2 weeks is recommended. Following this lead-in dose, a dose escalation (maintenance dose) to 200 mg nevirapine twice daily may be carried out in the absence of any hypersensitivity reactions (e.g. rash or liver function test abnormalities).

9.2 Treatment duration

Treatment duration is life-long – or until adverse effects, contraindications or viral resistance mandates a change of therapy.

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 WHO Guidelines also state that nevirapine is associated with a higher incidence of rash than efavirenz, and the rash may be severe and life-threatening. In addition, nevirapine is also associated with a rare but potentially life-threatening risk of hepatotoxicity, which makes the drug less suitable for patients using other hepatotoxic medications. Nevirapine is the preferred NNRTI for women if there is potential for pregnancy or during the first trimester of pregnancy, however it should be used in caution in women with CD4 cell counts between 250-350 cells/mm^3.

The 2006 US Department of Health and Human Services (DHHS) Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents[4] 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 review 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 we have taken the view 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 it was assumed that, if the FDC products have been approved after a suitable rigorous evaluation (eg 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 AZT/3TC/ NVP with other HIV regimens. The search terms used were:

1. zidovudine
2. lamivudine
3. nevirapine
4. 1 and 2 and 3
5. 4 and generic
6. 4 and toxicity
7. 4 and adverse events
8. 4 and randomised controlled trial

10.1.2 Systematic reviews identified

No relevant systematic reviews were identified. Note: a Cochrane review of dual therapy with AZT and 3TC is available and is covered in the parallel application for listing of the dual drug combination.

10.1.3 Selection/exclusion of particular data

There are no randomised comparative trials, nor any non-randomised studies, directly examining the efficacy and safety of fixed-dose combination AZT/3TC/NVP. There are however comparative trials assessing the fixed-dose combination of AZT/3TC with nevirapine added-on, or assessing the co-administration of AZT 3TC and NVP as separate components (see table 10.1.3.1). These trials have been included in order to provide an estimate of the efficacy and safety of the FDC of AZT/3TC/NVP. There is one observational study which has evaluated fixed dose formulations of NVP-based combinations including AZT/3TC/NVP; however results were provided only for all treatments together and AZT/3TC/NVP appears to have been a less commonly used combination (Pujari et al 2004).

Table 10.1.3.1 lists the trials presented.

Table 10.1.3.1: Selected data

Trial	Design
Randomised comparative trials	
French et al., 2002[5]	•randomised, open-label trial comparing triple combination therapies AZT/3TC/NVP, 3TC/d4T/NVP, d4T/ddl/NVP in treatment-naïve HIV patients (this trial is also considered in the submission for d4T/3TC/NVP). •trial duration 52 weeks
Podzamczer et al., 2002[6]	•randomised, open-label multicentre trial comparing AZT/3TC combined with either NVP or nelfinavir in treatment-naïve HIV patients (the Combine Study) •trial duration 12 months
Casado et al., 2007[7]	•subgroup analysis of Combine Study (a randomised, open-label multicentre trial comparing AZT/3TC combined with either NVP or nelfinavir (Podzamczer et al., 2004)), assessing health-related quality of life
Plana et al., 2004[8]	•substudy of immunological outcomes in the Combine Study, a randomised, open-label multicentre trial comparing AZT/3TC plus NVP or nelfinavir
Bonjoch et al., 2005[9]	•randomised, open-label, multicentre comparison of fixed dose combination of ABC/3TC/AZT and AZT/3TC plus NVP in HIV patients •trial duration 48 weeks

10.2 Summary of available data

10.2.1 Appraisal of quality

The table below provides an assessment of trial quality of the randomised trials.

Table 10.2.1.1: Assessment of quality of trials presented in the application

Trial	Done	Comments
French et al., 2002		
randomisation	✓	
blinding		•open-label trial
concealment of treatment allocation		NR
inclusion of all randomised participants in analysis (ITT)	✓	
generation of allocation sequences		•equal allocation, no information of how this was done
description of withdrawals	✓	
objective outcomes	✓	
Podzamczer et al., 2002		
randomisation	✓	•central randomisation
blinding		•open-label trial
concealment of treatment allocation		NR
inclusion of all randomised participants in analysis (ITT)	✓	
generation of allocation sequences		NR
description of withdrawals	✓	

Trial	Done	Comments
objective outcomes	✓	
Casado et al., 2004		
Randomisation	✓	•stratified by plasma HIV RNA and by CD4 cell count
Blinding		•open-label trial
concealment of treatment allocation		NR
inclusion of all randomised participants in analysis (ITT)	✓	
generation of allocation sequences		NR
description of withdrawals	✓	
objective outcomes	✓	
Plana et al., 2004		
Randomisation	✓	
Blinding		•open-label trial
concealment of treatment allocation		NR
inclusion of all randomised participants in analysis (ITT)	✓	
generation of allocation sequences		NR
description of withdrawals		NR
objective outcomes	✓	
Bonjoch et al., 2005		
Randomisation	✓	•centrally randomised
Blinding		•open label trial
concealment of treatment allocation		NR
inclusion of all randomised participants in analysis (ITT)	✓	
generation of allocation sequences		NR
description of withdrawals	✓	
objective outcomes	✓	

NR=not reported

10.2.2 Outcome measures

Table 10.2.2.1 provides the outcome measures used in the randomised trials.

Table 10.2.2.1: Outcome measures used in the trials

Trial/study	Outcomes
Randomised trials	
French et al., 2002	Primary outcomes: •time-weighted mean change from baseline in plasma HIV RNA at week 52 •proportion of patients with real-time HIV RNA <500 copies/mL at week 52 proportion of patients with stored plasma HIV RNA <50 copies/mL at week 52 Secondary outcomes: •quality of life scores
Podzamczer et al., 2002	Primary outcomes: •Proportion of patients with a plasma HIV-1 RNA (pVL) of < 200 copies/mL by PCR at 12 months.

Trial/study	Outcomes
	•changes in CD4 counts •clinical progression and adverse events Secondary outcomes: •proportion of patients with HIV RNA <20 copies/mL •changes in CD4 cell counts •occurrence of HIV-related complications and discontinuation due to adverse events
Casado et al., 2004	Primary outcome: •difference between treatment groups in health-related quality of life (HRQoL)
Plana et al., 2004	Primary outcomes: •change in viral load (VL), T-cell subsets and T-cell functions were analysed at baseline and after 1 year of treatment
Bonjoch et al., 2004	Primary outcomes: •Proportion of patients with plasma HIV-1 RNA <200 copies/mL at week 48 of follow-up Secondary outcomes: •Proportion of patients with plasma HIV-1 RNA <50 copies/mL at week 48 •evolution of CD4 counts •change of lipid metabolism and body shape, •safety profile of regimens •patient quality of life, adherence and satisfaction with the ongoing antiretroviral treatment

10.2.3 Summary of results – randomised trials

Table 10.2.3.1 provides the baseline demographic characteristics of the patients in the French et al (2002) trial.

Table 10.2.3.1: Baseline demographic characteristics in French et al (2002)

Characteristic	All patients (n=70)
Gender (% male)	59%
Mean age (years)	37
Mean CD4 count (cells/microL)	399
Prior AIDS	n=6

The results of the French et al (2002) trial are presented in Table 10.2.3.2 for the AZT/3TC/NVP versus 3TC/d4T/NVP comparison.

Table 10.2.3.2: Systematic review - results of French et al (2002) – 3TC/d4T/NVP versus AZT/3TC/NVP

	3TC/d4T/NVP		AZT/3TC/NVP			
Outcome	**N**	**Mean**	**N**	**Mean**	**WMD (95% CI)**	**p value**
Time-weighted reduction in real-time HIV RNA (log copies/mL)	21	-1.04	19	-1.17	0.13 (-0.52, 0.78)	0.7
Time-weighted reduction in stored HIV RNA (log copies/mL)	19	-2.16	15	-1.29	-0.87 (-1.68, -0.06)	0.04
Time-weighted change in CD4 count (cells/uL)	22	113.0	20	139.0	-26.0 (-106.7, 54.7)	0.5
	N	**n/N**	**N**	**n/N**	**RR (95% CI)**	**p value**
Undetectable real-time HIV RNA <500 copies/mL	22	15/22	23	14/23	1.12 (0.73, 1.73)	0.6
Undetectable stored HIV RNA <500 copies/mL	22	13/22	23	11/23	1.24 (0.74, 2.14)	0.5

3TC=lamivudine; d4T=stavudine; NVP=nevirapine; AZT=zidovudine

There was a statistically significant advantage for AZT/3TC/NVP compared to 3TC/d4T/NVP in reduction in stored HIV RNA. There were no other statistically significant differences between the treatment groups. The French et al (2002) trial reported that quality of life (QoL) measured by both patients and physicians was high at the beginning of the trial and remained high throughout the trial, with no statistically significant differences between the groups. The French et al (2002) paper did not provide any details regarding the QoL measure used nor the changes in the measures.

Table 10.2.3.4 provides the baseline demographic characteristics of the patients in the Podzamczer et al (2002) trial (the Combine Study), which compared AZT/3TC/NVP to AZT/3TC/NFV in treatment-naive HIV patients.

Table 10.2.3.3: Baseline demographic characteristics in the Podzamczer et al (2002) trial

Characteristic	AZT/3TC/NFV (n=70)	AZT/3TC/NVP (n=72)	p-value
Age Mean (Range)	35 (20-67)	36 (22-62)	>0.2
Men n (%)	47 (67.1)	59 (81.9)	0.043
Women n (%)	23 (32.9)	13 (18.1)	
Risk Practice n (%)			0.013
• Drug Users,	28 (40)	29 (40.3)	
• Homosexuals	13 (18.6)	27 (37.5)	
• Heterosexuals	22 (31.4)	15 (20.8)	
• Other	7 (10)	1 (1.4)	
CD4 cell (x µl)			
• Mean (range)	347 (20-777)	375 (10-908)	>0.2
• Median	351	361	>0.2
HIV RNA			>0.2
▪ (mean log_{10})	5.21	5.07	
▪ (mean copies/mL)	164,956	118,466	

3TC=lamivudine; NVP=nevirapine; AZT=zidovudine; NFV= nelfinavir.

The results of the Podzamczer et al (2002) trial are provided below.

Table 10.2.3.4 : Results of the Podzamczer et al (2002) – AZT/3TC/NFV vs. AZT/3TC/NVP

Outcome	AZT/3TC/NFV % (95% CI)	AZT/3TC/NVP % (95% CI)	p-value
Proportion of patients with a plasma HIV-1 RNA (pVL) of < 200 copies/mL by PCR at 12 months.	60% (48.5, 71.5)	75% (65, 85)	0.06
Proportion of patients with a plasma HIV-1 RNA (pVL) of < 20 copies/mL by PCR at 12 months	50% (38.3, 61.7)	65% (54.2, 76.2)	0.06
Discontinuation	21%	25%	
	Cells/mm^3	**Cells/mm^3**	
Changes in CD4 counts	+173 (p=0.08 vs. baseline)	+162 (p=0.01 vs. baseline)	NS

3TC=lamivudine; NVP=nevirapine; AZT=zidovudine; NFV= nelfinavir.

There were no statistically significant differences between the treatment groups for HIV-RNA outcomes, although there was trend to achieve greater suppression of HIV-1 RNA levels with AZT/3TC/NVP than with the NFV combination. There was a statistically significant advantage for AZT/3TC/NVP compared to baseline in raising CD4 cell counts, although there was no statistically significant advantage between the treatment groups. Based on the results of this trial, the efficacy of AZT/3TC/NVP and AZT/3TC/NFV appear similar.

Table 10.2.3.5 provides the baseline demographic characteristics of the Casado et al (2004) trial. This trial used a subset of patients in the Combine Study (Podzamczer et al., 2002) trial and assessed health-related quality of life (HRQoL) outcomes.

Table 10.2.3.5: Baseline demographic characteristics in the Casado et al (2004) trial: AZT/3TC/NFV vs. AZT/3TC/NVP.

Characteristic	AZT/3TC/NFV (n=63)	AZT/3TC/NVP (n=64)	p-value
Age Mean (Range)	36 (21-67)	38(26-62)	0.14
Sex Men n (%)	43 (68.3%)	51 (79.7%)	0.14
Risk Practice n (%)			0.08
• Drug Users,	26 (41.3%)	29 (45.3%)	
• Homosexuals	11 (17.5%)	21 (32.8%)	
• Heterosexuals	20 (31.7%)	13 (20.3%)	
• Other	6 (9.6%)	1 (1.6%)	
CD4 cell (x µl)			
• Mean (range)	353 (20-777)	364 (10-908)	0.75
• Median	355	348	0.39
HIV RNA			
▪ (mean $\log_{10}$)	4.82	4.69	0.24
▪ (mean copies/mL)	171,313	104,016	

3TC=lamivudine; NVP=nevirapine; AZT=zidovudine; NFV= nelfinavir

There were no statistically significant differences were observed at baseline in demographic and clinical variables and HRQoL scores between treatment groups.

The mean change from baseline to 12 months in MOS-HIV dimension and effect size are in the Casado et al (2004) trial are provided in Table 10.2.3.6.

Table 10.2.3.6: Results of the Casado et al (2004) trial: AZT/3TC/NFV vs. AZT/3TC/NVP

	AZT/3TC/NFV			AZT/3TC/NVP		
MOS-HIV dimension	**Mean change**	**Effect size**	**p value**	**Mean change**	**Effect size**	**p value**
General health perceptions	5.55	0.22	0.32	13.6	0.61	0.01
Pain	2.35	0.10	0.07	7.72	0.32	0.07
Physical functioning	-3.07	-0.20	0.37	6.03	0.26	0.07
Role functioning	5.83	0.20	0.17	12.22	0.32	0.03
Social functioning	-0.12	-0.01	0.64	5.25	0.21	0.10
Mental health	13.29	0.57	0.02	6.54	0.31	0.18
Energy/fatigue	7.72	0.34	0.20	10.06	0.42	0.02
Health distress	13.21	0.48	0.03	8.09	0.32	0.12
Cognitive function	5.51	0.27	0.40	9.3	0.34	0.19
Quality of life	8.1	0.39	0.004	15.0	0.73	0.01
Health transition	3.06	0.15	0.47	5.14	0.25	0.05
Physical health summary	-1.37	-0.15	0.52	5.78	0.51	0.005
Mental health summary	3.48	0.31	0.12	4.44	0.45	0.07

3TC=lamivudine; NVP=nevirapine; AZT=zidovudine; NFV= nelfinavir.

Differences in HRQoL between treatment groups were not detected. A trend towards improvement was observed in summary health scores in AZT/3TC/NVP-treated patients.

There were no statistically significant differences for CD4 cell count and viral load at 12 months between the treatment groups. Table 10.2.3.7 provides the mean CD4 and viral load values at 12 months.

Table 10.2.3.8: Results of the Casado et al (2004) study: CD4 and viral load at 12 months

Outcome	**AZT/3TC/NFV**	**AZT/3TC/NVP**
CD4 cell count cells/mm^3	157	185
Proportion with HIV RNA <200 copies/mL	83%	92%
Proportion with HIV RNA <20 copies/mL	70%	78%

NR=not reported; 3TC=lamivudine; NVP=nevirapine; AZT=zidovudine; NFV= nelfinavir

Table 10.2.3.8 provides the baseline demographic characteristics of patients in the Plana et al (2004) trial. This trial was an immunological substudy of the Combine Study (Podzamczer et al., 2002) and assessed the degree of immune recovery when antiretroviral therapy is started at intermediate stages of HIV infection.

Table 10.2.3.8: Baseline demographic characteristics in Plana et al (2004) study: AZT/3TC/NFV vs. AZT/3TC/NVP.

Characteristic	**All patients (n=36)**
Gender (n(%) male)	24 (67%)
Age (mean)	36
CD4 cell count (mean (cells/mm^3))	360
Viral load (mean (copies/mL))	173,895
Viral load (mean (log_{10}))	4.8

Table 10.2.3.9 provides the results of the Plana et al (2004) trial.

Table 10.2.3.9: Results of the Plana et al (2004): AZT/3TC/NFV vs. AZT/3TC/NVP

Outcome	AZT/3TC/NFV	AZT/3TC/NVP
Proportion with viral load<200 copies/mL	78%	83%
CD4 T cell count at 12 months	478 (p=0.021 vs. baseline)	584 (p=0.001 vs. baseline)
Percentage CD4 T cell at 12 months	28.11% (NS vs. baseline)	31.43% (NS vs. baseline)

NS=not significant; 3TC=lamivudine; NVP=nevirapine; AZT=zidovudine; NFV= nelfinavir

Both treatments significantly increased CD4 T cells at one year, with similar proportions of patients achieving viral load <200 copies/mL Overall, immune restoration achieved after 1 year of therapy with either NFV or NVP was similar.

Table 10.2.3.10 provides the baseline demographic characteristics of the Bonjoch et al (2005) trial, which examined virologic suppression in patients treated with AZT/3TC/NVP or AZT/3TC/ABC.

Table 10.2.3.10: Baseline demographic characteristics in Bonjoch et al (2005): AZT/3TC/NVP vs. AZT/3TC/ABC

Characteristic	All patients (n=134)	
Gender (% male)	82%	
Median age (years)	39	
	AZT/3TC/ABC (n=68)	AZT/3TC/NVP (n=66)
CD4 count (median (cells/mL))	530	554
% receiving PIs at inclusion in the study	89%	94%

3TC=lamivudine; NVP=nevirapine; AZT=zidovudine; ABC=abacavir

Table 10.2.3.11 provides the results of the Bonjoch et al (2004) trial following 48 weeks of treatment.

Table 10.2.3.11: Results of the Bonjoch et al (2004) study: AZT/3TC/NVP vs. AZT/3TC/ABC

Outcomes	AZT/3TC/ABC	AZT/3TC/NVP	RD (95% CI)
Proportion with plasma HIV-1 RNA <200 copies/mL	71%	73%	-2.1% (-17.4, 13.1)
Proportion with plasma HIV-1 RNA <50 copies/mL	65.1%	63.2%	1% (-15.1, 17.3)
Median increase in CD4 count from baseline	96 cells/uL	43 cells/uL	NR

3TC=lamivudine; NVP=nevirapine; AZT=zidovudine; ABC=abacavir

Results of the Bonjoch et al (2004) trial show that there were no statistically significant differences between the treatment groups in viral suppression.

10.3 Summary of available estimates of comparative effectiveness

Unlike with the parallel submission for d4T/3TC/NVP the clinical trial evidence for AZT/3TC/NVP is not well supplemented by observational data collected in low and middle income countries. In addition, the data relate to co-administration of the separate components of the FDC or partial FDC (ie,

AZT/3TC) plus NVP in separate tablet and not the FDC itself. Nevertheless, the clinical trial data provide convincing evidence of efficacy in relation to standard measures. The combination of AZT/3TC/NVP appears to be as effective as d4T/3TC/NVP and is probably at least as well tolerated. In addition, the results showed a trend to superior efficacy of the NVP combination compared with the same drugs combined with a protease inhibitor. These results are consistent with a recently published meta-analysis of direct head to head trials of NNRTI based combinations compared with protease-inhibitor based combinations, which found the former to be superior in terms of virological suppression and adverse effects.[11]

11. Summary of comparative evidence on safety

11.1 Estimate of total patient exposure to date

Estimates of total patient exposure are not available. As noted earlier, around 1.65 million people with HIV are now under treatment in low and middle income countries and it is likely that a large proportion of these are using fixed dose combinations, including AZT/3TC/NVP. This is likely to be less than use of the d4T/3TC/NVP fixed dose combination because of the earlier availability of the latter. The observational study of Pujari et al (2004), described in the parallel submission for d4T/3TC/NVP, states that around 20% of the study participants were taking AZT/3TC/NVP.

11.2 Description of adverse effects/reactions

Table 11.2.1 provides a summary of adverse events observed in the Combine Study (Podzamczer et al., 2002).

Table 10.2.3.6: Adverse events in the Combine Study (Podzamczer et al., 2002)

	AZT/3TC/NFV			AZT/3TC/NVP		
Adverse event	**N (%)**	**Grades I/II**	**Grades III/IV**	**N (%)**	**Grades I/II**	**Grades III/IV**
Diarrhoea	25 (35.7%)	22	3	0 [1]	0	0
Vomiting	7 (10.0%)	7	0	2 (2.7%)	2	0
Nausea	7 (10.0%)	7	0	5 (6.9%)	5	0
Other gastrointestinal	8 (11.4%)	7	1	6 (8.3%)	6	0
Asthenia	5 (7.1%)	5	0	2 (2.7%)	2	0
Depression/anxiety	4 (5.7%)	3	1	2 (2.7%)	2	0
Rash	1 (1.4%)	1	0	10 (13.9%) [2]	9	1
Other	5 (7.1%)	5	0	8 (11.1%)	8	0

3TC=lamivudine; NVP=nevirapine; AZT=zidovudine; ABC=abacavir
[1] p <0.0001
[2] p=0.005

Patients completed a questionnaire assessing lipodystrophy syndrome. No cases of body changes in either treatment group were reported. There was a statistically significant increase in fasting cholesterol levels in both treatment groups combined at 12 months, but there was no statistically significant difference between the groups. There was a statistically significant increase in triglyceride levels in the AZT/3TC/NFV arm compared to the AZT/3TC/NVP arm at 12 months (1.8 versus 1.4 mM/l; p=0.028).

Table 11.2.2 provides a summary of adverse events in Casado et al (2004).

Table 10.2.3.9: Adverse events in Casado et al (2004)

Outcome	AZT/3TC/NFV	AZT/3TC/NVP
Discontinued due to AE	14 (22.2%)	17 (26.6%)
Reason for discontinuation	•diarrhoea/vomiting: 11 •rash: 1 •increased ALAT: 1 •neutropenia: 1	•vomiting: 1 •rash: 4 •increased ALAT: 6 •neutropenia/anaemia: 6

3TC=lamivudine; NVP=nevirapine; AZT=zidovudine; NFV= nelfinavir

There were more discontinuations due to diarrhoea/vomiting in the AZT/3TC/NFV group compared to the AZT/3TC/NVP group, while the AZT/3TC/NVP group had more discontinuations due to rash, increased ALT and neutropenia.

The Plana et al (2004) trial did not report any adverse event data. In the Bonjoch et al (2005) trial, 13 patients (19.1%) in the AZT/3TC/NFV group and 14 patients (21.2%) in the AZT/3TC/NVP group discontinued treatment due to toxicity. The most frequent adverse event on both groups was rash (5 patients in each group). Grade 3 or 4 toxicity was observed in one patient in the AZT/3TC/NFV group (anaemia) and 4 patients in the AZT/3TC/NVP group (3 clinical hepatitis and 1 rash). No new cases of lipodystrophy were observed in either group.

The general literature on use of ARV drugs emphasises the occurrence of anemia with combinations that include zidovudine. As a result the WHO Guidelines recommend the availability of hemoglobin testing during treatment with the drug. In practice such facilities are widespread even in resource poor settings.

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 rash was observed in patients treated with nevirapine. Anemia is a well recognised consequence of treatment with zidovudine.

The WHO Guidelines[3] state that a higher incidence of rash is associated with nevirapine compared to efavirenz, and nevirapine is also associated with a rare but potentially life-threatening risk of hepatotoxicity. The Guidelines recommend that in the case of severe hepatic or skin reactions nevirapine should be permanently discontinued and not re-started. The Guidelines also recommend that NVP should be used with caution in women with CD4 counts between 250-350 cells/mm^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/NVP ranges from $0.21 (Nigeria) to $0.56 (Mozambique), with the average cost of treatment ranging from $155 to $411 per patient per year. The weighted average price of AZT/3TC/NVP in 2005 in low income countries was $USD156 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 $US 1100 and 1800.[12] Any value like this will be sensitive to the costs that were included in the model and the prices paid for ARV therapy. A judgement about cost-effectiveness is very context specific and will depend heavily on the perspective of the payer. A more recent study from the University of Capetown in South Africa (Cleary et al 2004. http://www.hst.org.za/uploads/files/arv_cost.pdf)[13] used a Markov model to simulate the outcomes and costs of introducing ARV therapy into a South African township. The study included a wide range of direct costs, but no productivity gains resulting from effective treatment. The treatment scenarios used in this study did not include a fixed dose combination pf AZT/3TC/NVP but did include d4T/3TC/NVP, which has a similar efficacy and price. The model used by the investigators also included the use of an alternative non-nucleoside transferase inhibitors, efavirenz and other second line drugs, which are more expensive. This study included a range of direct costs, including anti-retroviral drugs at an average annual purchase cost of 4000 to 5000 Rand ($US 550 – 700), which is substantially higher than the international prices for a FDC product containing AZT/3TC/NVP. 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/NVP as recorded in the WHO drugs database (2005)[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/NVP has been registered and the information confirmed by the national drug regulatory authority include 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.

Table 13.1 – Regulatory status as based on WHO drugs database

INN and dosage	Manufacturer and country	Countries that have granted registration
lamivudine150mg + zidovudine 300mg + nevirapine 200mg tablet.	Cipla Ltd, India	Benin, Gambia, Mauritania, Nigeria, Sierra, Leone, Uganda, Zambia.
	Ranbaxy Ltd, India	India.
	Hetero Drugs, India	Burundi, Congo, Gambia, India, Kenya, Malawi, Nigeria.
	Aurobindo	WHO prequalified, India
	Emcure, India	India
	Apotex Inc, Canada[a]	WHO prequalified
lamivudine150mg + zidovudine 300mg tablet plus nevirapine 200mg tablet (Co-pack)	Aspen, South Africa	WHO prequalified, USA FDA Pre-Approved, South Africa

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

Source: http://ftp.who.int/htm/AMDS/drugsdatabase.pdf

14. Availability of pharmacopoeial standards

The individual components that comprise the AZT/3TC/NVP fixed-dose combination tablet are listed in the European and the US Pharmacopoeias; however the fixed dose combination tablet is not listed in either. The individual drugs have also been included in the International Pharmacopoeia (details are at http://www.who.int/medicines/areas/quality_safety/safety_efficacy/mon_arvs/en/index.html); however, searches have not uncovered a monograph for the FDC either here or elsewhere.

15. Proposed text for the WHO Model Formulary

The proposed text for the WHO Model Formulary is provided in Attachment 1.

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