WHO MODEL LIST OF ESSENTIAL MEDICINES APPLICATION

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

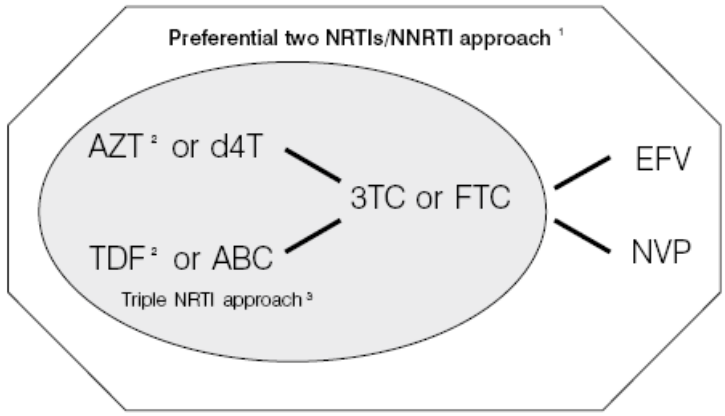
1. Summary statement of proposal for inclusion, change, or deletion

The combination tablet of stavudine/lamivudine/nevirapine (d4T/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 (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 d4T/3TC/NVP. The attractions of this combination are its efficacy (as reviewed in this submission), tolerability (see below), wide availability from multiple suppliers and low cost, wide practical experience with its use and safety data in a wide range of settings. Another widely used FDC comprising AZT/3TC and NVP is the subject of a separate submission. Other possible NRTI combinations comprising tenofovir (TDF) and emtricitabine (FTC) or lamivudine (3TC) are also appropriate but 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)

stavudine/lamivudine/nevirapine

5. Formulation proposed for inclusion

Combination tablet comprised of stavudine 30mg and lamivudine 150mg and nevirapine 200mg for patients weighing less than 60 kg, and combination tablet comprised of stavudine 40mg and lamivudine 150mg and nevirapine 200mg for patients weighing 60kg or above.

6. International availability

Section 13 (see Table 13.1) provides a list of the manufacturers. Two manufacturers, Cipla Ltd (India) and Ranbaxy Laboratories Limited (India) supply generic 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 (stavudine 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	1,700,000	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 estimates of the number of people receiving antiretroviral (ART) therapy in developing countries in specific regions.

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 combined antiretroviral (HAART) therapy has resulted in a decline in mortality in both the developed and developing world[2]. The WHO Guidelines on "Antiretroviral Therapy for HIV Infection in Adults and Adolescents" (2006 revision) recommend a combination of two NRTI and one NNRTI as the preferred first-line option in developing countries (resource-poor)[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). The WHO has stated that, given the wide availability of suitable fixed dose combinations, d4T-containing regimens may still remain the most accessible option for people in urgent need of treatment in resource-limited settings in the short to medium-term. This is despite some concerns about adverse effects (See Section 11.4). Thus, inclusion of the fixed dose combination of d4T/3TC/NVP on the WHO Model List is sought. Evidence demonstrating the efficacy and safety of d4T/3TC/NVP is provided in Section 10.2 and Section 11.

8.2 Assessment of current use

Combination treatment with lamivudine, stavudine and nevirapine is considered a standard first-line treatment for HIV infection and is widely used world-wide. It is one of the most frequently prescribed treatments in African countries (Laurent et at., 2004) and is used in a national ARV treatment program initiated in 2002 in Nigeria (Idigbe et al., 2005). The use of a generic combination product has been assessed in a number of resource-poor countries (see Section 10.2.4).

8.3 Target population

Patients with HIV infection.

9. Treatment details

9.1 Dosage regimen

The Product Information recommends that for the first two weeks of therapy, the three components should be taken separately, as one 200mg nevirapine tablet once daily, and stavudine and lamivudine twice daily. If no rash or other side effects occur, treatment with the combined form may begin. The recommended dose of d4T/3TC/NVP is one tablet twice daily, with or without food. The fixed combination with 30mg stavudine is for patients weighing less than 60kg, and the fixed dose combination tablet with 40mg stavudine is for patients weighing 60kg or above.

9.2 Treatment duration

Treatment duration is continuing or until treatment has to be changed because of adverse effects, contraindications or development of viral resistance to the component drugs.

9.3 Reference to WHO and other clinical guidelines

The WHO guidelines on "Antiretroviral Therapy for HIV Infection in Adults and Adolescents" (2006 revision)[3] include a d4T/3TC/NVP regimen in the recommendations for first-line therapy. However, the Guidelines note that stavudine (d4T) has been associated with lactic acidosis, lipoatrophy and peripheral neuropathy, that these toxicities are cumulative and often irreversible, and have the potential to affect adherence in the long-term. The Guidelines also state that "WHO notes that it is important to begin planning to move away from d4T-containing regimens so as to avoid or minimize the predictable toxicities associated with this drug" (Section 5.4, p21 of the WHO Guidelines).

The WHO Guidelines (2006) 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 when there is a potential for pregnancy, or during the first trimester of pregnancy.

The 2006 US Department of Health and Human Services (DHHS) Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents[5] recommend that stavudine and lamivudine only be used in combination with a NNRTI when the preferred or alternative dual-NRTI combinations cannot be used, due to the toxicity associated with these drugs.

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 is also 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 d4T/3TC/NVP with other HIV regimens. The search terms used were:

1. stavudine
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

One Cochrane systematic review was identified (Siegfried et al 2006). This review assessed d4T/3TC/NVP for the treatment of HIV infection and AIDS in adults (see Section 9.2.3).

10.1.3 Selection/exclusion of particular data

Trials were included if they were randomised controlled trials of d4T/3TC/NVP compared to another HIV regimen in adult patients. As a recent systematic review (Siegfried et al., 2006) is available, and all selected trials were included in this review, it is the main evidence base for this application.

To provide an assessment of the use and effectiveness of d4T/3TC/NVP in resource-poor settings, non-randomised observational studies were also included. The inclusion of these non-randomised studies is important as they should reflect 'real world' experience of treatment in resource poor settings and all but one (Idigbe et al 2005) most employed the fixed dose combination under consideration; the randomised trials appear to have used concomitant treatment with the component drugs.

Table 10.1.3.1 lists the reviews and studies that are included in the submission.

Table 10.1.3.1: Selected data

Trial	Design
Systematic reviews of randomised trials	
Siegfried et al., 2006[6] (Cochrane review)	•systematic review of efficacy of d4T/3TC/NVP for treatment of HIV infection and AIDS in adults •including randomised controlled trials comparing d4T/3TC/NVP either to placebo or any other antiretroviral regimen
Non-randomised studies	
Calmy et al., 2006[7]	•observational cohort study of adult HIV patients in 21 Medecins Sans Frontieres (MSF) HIV/AIDS treatment programs using d4T/3TC/NVP
Pujari et al., 2004[8]	•observational study of generic fixed-dose combination drugs in treatment-naive adult HIV patients in India •treatments included AZT/3TC/NVP and d4T/3TC/NVP
Idigbe et al., 2005[9]	•observational cohort study of ARV-naive adult patients in Nigeria •patients were treated with 3TC 150mg/d4T 40mg/NVP 200mg twice daily
Laurent et al., 2004[10]	•open-label, one-arm multicentre trial of adult HIV patients in Cameroon •patients treated with 3TC 150mg/d4T 30mg if weight <60kg otherwise 40mg/NVP 200mg twice daily for 24 weeks
Anekthananon et al., 2004[11]	•open-label, one-arm study of d4T/3TC/NVP in advanced HIV patients in Thailand •24 week duration
Tin et al., 2005[12]	•retrospective and prospective study of d4T/3TC/NVP in treatment-naïve adult patients in Thailand •one year duration
van Oosterhout et al., 2005[13]	•retrospective study of d4T/3TC/NVP in adult HIV patients in Malawi

The Cochrane systematic review included two randomised trials, French et al., 2002 and van Leth et al., 2004. The French et al (2002) trial was a randomised, open-label trial comparing zidovudine, lamivudine and nevirapine (AZT/3TC/NVP) twice daily, d4T/3TC/NVP twice daily and didanosine, stavudine and nevirapine (ddl/d4T/NVP) twice daily in treatment-naive adult patients. Treatment duration was 52 weeks and 70 patients were randomised. The van Leth et al (2004) trial was a randomised, open-label multicentre trial comparing d4T/3TC twice daily combined with NVP 400mg once daily, d4T/3TC twice daily combined with efavirenz (EFZ) 600mg once daily, d4T/3TC twice daily combined with EFZ 800mg and NVP 400mg once daily. An additional group treated with d4T/3TC twice daily combined with NVP 200mg twice daily was added after five months. Treatment duration was 48 weeks and 1216 patients were randomised. Patients were recruited from Argentina, Australia, Belgium, Brazil, Canada, France, Germany, Greece, Ireland, Italy, Poland, Portugal, South Africa, Switzerland, Thailand, UK and the US.

10.2 Summary of available data

10.2.1 Appraisal of quality

The table below provides an assessment of the methodological quality of the two trials included in the systematic review. As this assessment focuses on the quality of randomised trials, the non-randomised studies are not included.

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		
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	✓	
van Leth et al., 2004		
Randomisation	✓	
Blinding		•open-label trial
concealment of treatment allocation	✓	
inclusion of all randomised participants in analysis (ITT)	✓	
generation of allocation sequences	✓	•central study coordination centre, concealed from investigator
description of withdrawals	✓	
objective outcomes	✓	

10.2.2 Outcome measures

Table 10.2.2.1 provides the outcome measures used in the two randomised trials included in the systematic review and the outcomes used in the non-randomised studies.

Table 10.2.2.1: Outcome measures used in the trials and observational studies

Trial/study	Outcomes
Systematic review (Siegfried et al., 2006)	
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
van Leth et al., 2004	Primary outcomes: •proportion of patients with treatment failure, defined as a composite endpoint consisting of 1) decline of <1 log10 in plasma HIV RNA

Trial/study	Outcomes
	within first 12 weeks or two consecutive measurements >=50 copies/mL from week 24 onward; 2) CDC Grade C event from week 8 onward diagnosed according to published guidelines, or death; 3) non-allowable change of allocated treatment Secondary outcomes: •proportion of patients with virological failure (never having a plasma HIV RNA concentration <50 copies/mL or to consecutive measurements >= 50 copies/mL after having had a concentration below the cutoff •proportion of patients with plasma HIV RNA concentrations <50 copies/mL at each study week •change in CD4-positive cells between start of treatment and week 48
Non-randomised studies	
Calmy et al., 2006	•median change in CD4 cell count from baseline at 6, 12, and 18 months •probability of survival at 6, 12 and 18 months (Kaplan-Meier) •factors associated with progression to death (Cox proportional hazards models stratified by programme)
Pujari et al., 2004	•CD4 cell count measured quarterly, change in CD4 cell count at 12 and 24 months •occurrence of rash and hepatitis, with logistic regression analysis used to assess risk of development of rash and hepatitis with age, gender, baseline CD4 count, concomitant co-trimoxazole or antituberculosis therapy as independent variables •occurrence of clinical events
Idigbe et al., 2005	•change from baseline in viral load, CD4 cell count, body mass index and Karnofsky score
Laurent et al., 2004	Primary outcomes: •proportion of patients with plasma HIV RNA <50 and <400 copies/mL Secondary outcomes: •reduction in log10-transformed viral load from baseline •increase in CD4 cell count from baseline •incidence of disease progression •adverse events •genotypic mutations cumulative probability of remaining alive or free of news AIDS defining events
Anekthananon et al., 2004	•mean change in CD4 cell count and HIV RNA at week 24 •proportion with viral load <400 copies/mL •mean increase in CD4 cell count from baseline
Tin et al., 2005	•change in body weight •change in CD4 cell count •occurrence of opportunistic infections •occurrence of long-term side effects
van Oosterhout et al., 2005	•adherence to treatment •virological treatment failure (detectable viral load after minimum of 6 months of ART) •immunological treatment failure (<25% annual increase of baseline CD count) •clinical treatment failure (occurrence of AIDS defining event or pulmonary tuberculosis after minimum of 6 months of ART)

10.2.3 Summary of results – systematic review

The systematic review (Siegfried et al., 2006) did not pool data and reported the results of the two included trials separately, as they did not

use the same drug comparisons. Table 10.2.3.1 provides the baseline demographic characteristics of the patients in the 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 d4T/3TC/NVP versus AZT/3TC/NVP comparison and Table 10.2.3.3 for the d4T/3TC/NVP versus d4T/ddl/NVP comparison.

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

	d4T/3TC/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

Table 10.2.3.3: Systematic review - results of French et al (2002) – d4T/3TC/NVP versus d4T/ddl/NVP

	d4T/3TC/NVP		d4T/ddl/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	23	-1.60	0.56 (0.00, 1.12)	0.05
Time-weighted reduction in stored HIV RNA (log copies/mL)	19	-2.16	20	-1.78	-0.38 (-0.90, 0.14)	0.2
Time-weighted change in CD4 count (cells/uL)	22	113.0	23	174.0	-61.0 (-136.4, 14.4)	0.1
	N	**n/N**	**N**	**n/N**	**RR (95% CI)**	**p value**
Undetectable real-time HIV RNA <500 copies/mL	22	15/22	25	20/25	0.85 (0.60, 1.20)	0.4
Undetectable stored HIV RNA <500 copies/mL	23	13/23	25	16/25	0.88 (0.56, 1.40)	0.6

3TC=lamivudine; d4T=stavudine; NVP=nevirapine; ddl=didanosine

The first and most obvious comment is that this trial is very small. The treatment sample sizes are large enough to provide basic evidence of efficacy but are not large enough to enable a confident comparison of active treatments. There was an apparent statistically significant advantage for AZT/3TC/NVP compared to d4T/3TC/NVP in reduction in *stored* HIV RNA, and a statistically significant advantage for d4T/ddl/NVP compared to d4T/3TC/NVP in reduction in *real-time* 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 van Leth et al (2004) trial.

Table 10.2.3.4: Baseline demographic characteristics in the van Leth et al (2004) trial

Characteristic	d4T/3TC/bd and NVP/od (n=220)	d4T/3TC/NVP bd (n=387)	d4T/3TC/bd and EFZ/od (n=400)	d4T/3TC/bd NVP/EFZ od (n=209)
Gender (% male)	139 (63.2%)	236 (61.0%)	254 (63.5%)	143 (68.4%)
Mean age (years)	34.4	33.9	34.7	33.2
BMI (kg/m^2)	19.2	19.7	19.3	19.2
Geographical region				
Asia/Australia (n=223)	52 (23.6%)	52 (13.4%)	76 (19.0%)	43 (20.6%)
Europe (n=249)	50 (22.7%)	72 (18.6%)	78 (19.5%)	49 (23.4%)
South Africa (n=430)	72 (32.7%)	146 (37.7%)	141 (35.2%)	71 (34.0%)
South America (n=249)	40 (18.2%)	89 (23.0%)	84 (21.0%)	36 (17.2%)
North America (n=65)	6 (2.7%)	28 (7.2%)	21 (5.3%)	10 (4.8%)
CDC class C (number (%))	44 (20.0%)	86 (22.2%)	84 (21.0%)	39 (18.7%)
CD4 cell count				
Median cells/μL	200	170	190	190
Number (%) <50 cells/μL	35 (15.9%)	79 (20.4%)	70 (17.5%)	28 (13.4%)
Number (%) 50-200 cells/μL	76 (34.5%)	138 (35.7%)	144 (36.0%)	80 (38.3%)
Number (%) >200 cells/μL	109 (49.5%)	170 (43.9%)	186 (46.5%)	101 (48.3%)
HIV RNA				
Median log10 copies/mL	4.7	4.7	4.7	4.7
Number (%) <100,000	152 (69.1%)	264 (68.2%)	263 (65.8%)	139 (66.5%)
Number (%) >100,000	68 (30.9%)	123 (31.8%)	137 (34.3%)	70 (33.5%)
Co-infection				
Hepatitis B (number (%))	15 (6.8%)	17 (4.4%)	16 (4.0%)	16 (7.7%)
Hepatitis C (number (%))	22 (10.0%)	35 (9.0%)	40 (10.0%)	19 (9.1%)

3TC=lamivudine; d4T=stavudine; NVP=nevirapine; EFZ=efavirenz; bd=twice daily; od=once daily

Tables 10.2.3.5 to 10.2.3.9 provide the results of Siegfried et al (2006) for the van Leth et al (2004) trial.

Table 10.2.3.5: Systematic review - results of van Leth et al (2004) – d4T/3TC twice daily combined with NVP once daily versus d4T/3TC/NVP twice daily

	d4T/3TC/bd and NVP/od		d4T/3TC/NVP bd			
Outcome	N	n/N	N	n/N	RR* (95% CI)	p value
Treatment failure on or before week 48	220	96/220	387	169/387	1.00 (0.83, 1.21)	1.00
Undetectable plasma HIV RNA <50 copies/mL at week 48	220	157/220	387	253/387	1.09 (0.98, 1.22)	0.1
Death	220	7/220	387	9/387	1.37 (0.52, 3.62)	0.5

3TC=lamivudine; d4T=stavudine; NVP=nevirapine; bd=twice daily; od=once daily
*RR = risk of the event with d4T/3TC/bd and NVP/od compared with all drugs bd.

Table 10.2.3.6: Systematic review - results of van Leth et al (2004) – d4T/3TC twice daily combined with NVP once daily versus d4T/3TC twice daily combined with EFZ once daily

Outcome	d4T/3TC/bd and NVP/od		d4T/3TC/bd and EFZ/od		RR* (95% CI)	p value
	N	n/N	N	n/N		
Treatment failure on or before week 48	220	96/220	400	151/400	1.16 (0.95, 1.41)	0.1
Undetectable plasma HIV RNA <50 copies/mL at week 48	220	154/220	400	280/400	1.00 (0.90, 1.11)	1.00
Death	220	7/220	400	7/400	1.82 (0.65, 5.12)	0.3

3TC=lamivudine; d4T=stavudine; NVP=nevirapine; EFZ=efavirenz; bd=twice daily; od=once daily
*RR = risk of the event with d4T/3TC/bd and NVP/od compared with d4T/3TC/bd and EFZ od

Table 10.2.3.7: Systematic review - results of van Leth et al (2004) – d4T/3TC twice daily combined with NVP once daily versus d4T/3TC/twice daily combined with NVP/EFZ once daily

Outcome	d4T/3TC/bd and NVP/od		d4T/3TC/bd and NVP/EFZ od		RR* (95% CI)	p value
	N	n/N	N	n/N		
Treatment failure on or before week 48	220	96/220	209	111/209	0.82 (0.67, 1.00)	0.05
Undetectable plasma HIV RNA <50 copies/mL at week 48	220	154/220	209	131/209	1.12 (0.98, 1.28)	0.1
Death	220	7/220	209	2/209	3.33 (0.70, 15.82)	0.1

3TC=lamivudine; d4T=stavudine; NVP=nevirapine; EFZ=efavirenz; bd=twice daily; od=once daily
*RR = risk of the event with d4T/3TC/bd and NVP/od compared with d4T/3TC/bd and NVP/EFZ od

Table 10.2.3.8: Systematic review - results of van Leth et al (2004) – d4T/3TC/NVP twice daily versus d4T/3TC twice daily combined with EFZ once daily

Outcome	d4T/3TC/NVP bd		d4T/3TC/bd and EFZ/od		RR* (95% CI)	p value
	N	n/N	N	n/N		
Treatment failure on or before week 48	387	169/387	400	151/400	1.16 (0.98, 1.37)	0.09
Undetectable plasma HIV RNA <50 copies/mL at week 48	387	253/387	400	280/400	0.93 (0.85, 1.03)	0.2
Death	387	9/387	400	7/400	1.33 (0.50, 3.53)	0.6

3TC=lamivudine; d4T=stavudine; NVP=nevirapine; EFZ=efavirenz; bd=twice daily; od=once daily
*RR = risk of the event with d4T/3TC/bd and NVP/bd compared with d4T/3TC/bd and EFZ od

Table 10.2.3.9: Systematic review - results of van Leth et al (2004) – d4T/3TC/NVP twice daily versus d4T/3TC twice daily combined with NVP/EFZ once daily

Outcome	d4T/3TC/NVP bd		d4T/3TC/bd and NVP/EFZ od		RR* (95% CI)	p value
	N	n/N	N	n/N		
Treatment failure on or before week 48	387	169/387	209	111/209	0.82 (0.69, 0.97)	0.02
Undetectable plasma HIV RNA <50 copies/mL at week 48	387	253/387	209	131/209	1.04 (0.92, 1.18)	0.5
Death	387	9/387	209	2/209	2.43 (0.53, 11.14)	0.3

3TC=lamivudine; d4T=stavudine; NVP=nevirapine; EFZ=efavirenz; bd=twice daily; od=once daily
*RR = risk of the event with d4T/3TC/bd and NVP/bd compared with d4T/3TC/bd and NVP/EFZ od

Overall, in the van Leth (2004) trial there was little difference between the treatment arms. The main significance of the results, from the standpoint of the current application, is that nevirapine 200mg bd and 400mg od were equivalent, that nevirapine and efavirenz appeared equivalent and the combination of nevirapine and efavirenz with the two NRTIs was not superior to the use of either nevirapine or efavirenz in the combined treatment.

10.2.4 Summary of results – non-randomised studies

Table 10.2.4.1 provides the baseline demographic characteristics of the Calmy et al (2006) study, which assessed outcomes in patients in an observational cohort based on 21 MSF HIV/AIDS programs that employed the fixed dose combination of d4T/3TC/NVP. This is the largest of the observational studies reviewed here.

Table 10.2.4.1: Baseline demographic characteristics of Calmy et al (2006) study

Characteristic	**d4T/3TC/NVP (n=6961)**
Origin (number (%))	
Africa	5175 (75.4%)
Asia	1617 (23.6%)
Central America	69 (1.0%)
Gender (% female)	4210 (61.4%)
Median age	34
ARV-naive (number (%))	6025 (87.8%)
WHO stage (number (%)	
I/II	900 (13.1%)
III	3643 (53.1%)
IV	2318 (33.8%)
BMI	
Number assessed	6094
<18 kg/m2	1950 (32.0%)
≥18 kg/m2	4144 (68.0%)
Haemoglobin	
Number assessed	4646
<80 g/l	372 (8.0%)
80-99 g/l	1085 (23.3%)
>100 g/l	3189 (68.7%)
CD4 count	
Number assessed	4893
Median cells/μL	89
<50 cells/μL (number (%))	1620 (33.1%)

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

Table 10.2.4.2 provides the results of the Calmy et al (2006) study.

Table 10.2.4.2: Results of Calmy et al (2006)

Outcome	**d4T/3TC/NVP**
Treatment adherence at 1 year	5992/6861 (87.3%) at 4.1 months 503/655 (76.8%) 12 month sub-cohort
Rate of death	14.2/100 person-years (95% CI: 13.8, 14.5)
Probability of survival	**Probability of survival (95% CI)**
6 months	0.93 (0.92, 0.94)
12 months	0.90 (0.89, 0.91)

Outcome	d4T/3TC/NVP	
18 months	0.89 (0.87, 0.90)	
Probability of survival at 12 months by baseline CD cell count		
<15 cells/μL	0.81 (0.76, 0.85)	
15-50 cells/μL	0.86 (0.82, 0.89)	
50-99 cells/μL	0.94 (0.92, 0.96)	
100-199 cells/μL	0.94 (0.92, 0.96)	
>200 cells/μL	0.96 (0.93, 0.97)	
Factors associated with death	**Hazard ratio (95% CI)**	**p value**
Male	1.75 (1.34, 2.27)	<0.001
Age ≥35	1.25 (0.97, 1.61)	0.09
WHO stage III	2.07 (1.04, 4.12)	0.038
WHO stage IV	3.86 (1.93, 7.70)	<0.001
BMI <18	2.38 (1.82, 3.11)	<0.001
CD4 <15 cells/μL	3.63 (1.95, 6.75)	<0.001
CD4 15-49 cells/μL	2.54 (1.38, 4.67)	0.003
CD4 50-99 cells/μL	1.52 (0.80, 2.90)	0.20
CD4 100-199 cells/μL	1.26 (0.67, 2.36)	0.47
Haemoglobin <80 g/l	2.62 (1.80, 3.81)	<0.001
Haemoglobin 80-99 g/l	1.48 (1.09, 2.01)	0.012

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

The Calmy et al (2006) paper states that although the analysis did not include assessment of viral load or AIDS events, the clinical outcomes were satisfactory and consistent with results observed in other resource-poor settings (eg, Laurent et al., 2004). Serial measures of CD4 counts were available from a sub-set of individuals and showed a response to treatment. The median baseline count was 89 cells/ul, rising to 102 cells/ul @ 6 months (n=695), 144 cells/ul @ 12 months (n=209) and 173 cells/ul @ 18 months (n=45). Calmy et al (2006) claim that the relatively high death rate was likely to be due to undiagnosed opportunistic infections at the time of treatment initiation and/or the advanced stage of disease at treatment initiation.

Table 10.2.4.3 provides the demographic characteristics of patients in the Pujari et al (2004) study, which assessed the efficacy of generic d4T/3TC/NVP and AZT/3TC/NVP in treatment-naive patients in India.

Table 10.2.4.3: Baseline demographic characteristics of Pujari et al (2004) study

Characteristic	d4T/3TC/NVP or AZT/3TC/NVP (n=1253)
Median age (years)	36.5
Gender (% male)	77.8%
CD4 cell count cells/mm^3 (%)	79.5%
CD4 cell count <50 cells/mm^3 (%)	22.2%

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

Table 10.2.4.4 presents the increase in CD4 cell count observed in the Pujari et al (2004) study. The Pujari et al (2004) paper states that almost 80% of patients took d4T/3TC/NVP. As the paper provides results for all patients combined, the results below include patients (±20%) treated with AZT/3TC/NVP.

Table 10.2.4.4: Results of Pujari et al (2004) – increase in CD4 cell count

Time from starting treatment (months)	Number of patients	Increase in CD4 count from baseline (95% CI)
3	1253	150.2 (143.4, 157.0)
6	835	179.4 (170.8, 188.0)
9	372	204.3 (189.2, 219.4)
12	499	245.7 (230.6, 260.8)
15	174	255.3 (231.2, 279.4)
18	256	280.0 (255.5, 304.5)
21	74	281.3 (237.4, 328.8)
24	113	317.3 (277.6, 357.0)

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

There was a statistically significant increase in CD4 count at 12 months and 24 months following baseline ($p<0.001$). Pujari et al (2004) reported that patients reporting improvement in CD4 count reported more than 95% adherence to their regimen.

Table 10.2.4.5 provides the baseline demographic characteristics of patients in the Idigbe et al (2005) study, which assessed treatment with d4T/3TC/NVP in 50 HIV patients in Nigeria.

Table 10.2.4.5: Baseline demographic characteristics of Idigbe et al (2005) study

Characteristic	d4T/3TC/NVP (n=50)
Gender (% male)	44%
Median age (years)	34.5
Median CD4 count (cells $\times 10^6$/L)	260
Median HIV RNA (log_{10} copies/mL)	3.65
WHO stage (number (%))	
I	36 (72%)
II	14 (28%)
III	-
IV	-
Median BMI (kg/m^2)	21.64
Karnofsky score (number %))	
<70	-
70	8 (16%)
80	16 (32%)
90	24 (48%)
100	2 (4%)
Presented with opportunistic infections (%)	38%

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

Table 10.2.4.6 provides a summary of the results of the Idigbe et al (2005) study.

Table 10.2.4.6: Results of Idigbe et al (2005)

Outcome	Baseline	Endpoint	Median change	p value
Viral load (log_{10} copies/mL) – 24 weeks	3.65	2.30	-1.23	0.0000
Viral load (log_{10} copies/mL) – 24 weeks (excluding patients with viral load below detection at baseline and endpoint)	4.13	2.30	-1.79	0.0000
CD4 count ($\times 10^6$ cells/L) – week 12	260	360	100	0.0000
CD4 count ($\times 10^6$ cells/L) – week 24	260	370	110	0.0436

CD4 count ($\times 10^6$ cells/L) – week 48	260	445	186	0.0000
Proportion with Karnofsky score >90% - 12 weeks	52%	73%	NR	NR
Proportion with Karnofsky score >90% - 24 weeks	52%	88%	NR	NR
Proportion with Karnofsky score >90% - 48 weeks	52%	96%	NR	NR

NR=not reported

Idigbe et al (2005) report that >85% of patients had adequate adherence to drug intake. The authors conclude that the reduction in viral load is consistent with other reports from developing countries and demonstrates the efficacy of the treatment regimen.

Table 10.2.4.7 provides the demographic characteristics of the patients in the Laurent et al (2004) study, which assessed the use of generic d4T/3TC/NVP in HIV patients in Cameroon. A total of 61 patients were enrolled, with 60 being treated.

Table 10.2.4.7: Baseline demographic characteristics of Laurent et al (2004) study

Characteristic	**d4T/3TC/NVP (n=50)**
Gender (% female)	41 (68%)
Age (years)	34.5
BMI (kg/m^2)	23.1
Time since diagnosis of HIV seropositivity (months)	12.2
CDC clinical stage (number (%))	
A	10 (17%)
B	25 (42%)
C	25 (42%)
CD4 count (cells/μL)	118
Viral load (copies/mL)	104,736
Treatment-naive (number (%))	58 (97%)

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

Table 10.2.4.8 provides the results of the Laurent et al (2004) study. Analysis was on an intent-to-treat basis.

Table 10.2.4.8: Results of Laurent et al (2004)

Outcome	**Week 12**	**Week 24**
	Proportion (95% CI)	**Proportion (95% CI)**
HIV RNA <400 copies/mL	75% (62, 85)	80% (68, 89)
HIV RNA <50 copies/mL	45% (32, 58)	65% (52, 77)
	Log_{10} copies/mL (95% CI)	**Log_{10} copies/mL (95% CI)**
Median decline in viral load	3.0 (2.5, 3.5)	3.1 (2.5, 3.6)
	Cells/μL (95% CI)	**Cells/μL (95% CI)**
Median increase in CD4 count	NR	83 (40, 178)

The frequency of disease progression was 32.0/100 person-years (95% CI: 16.6, 61.5) and the incidence of AIDS-defining events was 14.2/100 person-years (95% CI: 5.3, 37.9). The rate of death was 17.8/100 person-years (95% CI: 7.4, 42.7). The cumulative probability of remaining alive or free of new AIDS-defining events after 24 weeks

was 0.85 (95% CI: 0.73, 0.92). The self-reported adherence rate was 99%. The authors conclude that the results demonstrate that the generic fixed-dose combination of d4T/3TC/NVP shows similar effectiveness to other HAART regimens and is at least as good as that obtained with HAART in industrialised countries.

Table 10.2.4.9 provides the results of the Anekthananon et al (2004) study of the use of d4T/3TC/NVP in advanced HIV patients in Thailand. A total of 101 patients were enrolled, treatment duration was 24 weeks and analysis was on an intent-to-treat basis. The mean baseline CD4 count was 58.7 cells/mm^3 and the mean baseline HIV RNA level was 5.3 $\log_{10}$ copies/mL.

Table 10.2.4.9: Results of Anekthananon et al (2004)

Outcome	Result
Mean decrease in HIV RNA $\log_{10}$ copies/mL	3.6 (95% CI: 2.70, 3.03; p<0.001)
Proportion with HIV RNA <400 copies/ml	80.2%
Increase in CD4 count (cells/mm^3)	96.5 (p<0.001)

There was a statistically significant decrease in HIV RNA and a statistically significant increase in CD4 cell count. The authors conclude that the fixed dose combination of d4T/3TC/NVP is effective in advanced HIV-infected patients in Thailand.

Table 10.2.4.10 summarises the results of the Tin et al (2005) study, which assessed the use of d4T/3TC/NVP in treatment-naive patients in Thailand. A total of 83 patients treated for at least one year were assessed.

Table 10.2.4.10: Results of Tin et al (2005)

Outcome	Results
Body weight	•52.3% had weight increase >10% after 12 months treatment
CD4 count	•median increase of 78 $\times$ 10^6 cells/L during first 3 months •39.5% achieved CD4 count >200 and 11.6% achieved CD4 count >500 after 2 years of treatment
Occurrence of opportunistic infections	•significantly lower after treatment (p=0.001)

Although little information is available regarding this study, the available results demonstrate efficacy of d4T/3TC/NVP in treatment-naive patients in Thailand.

Table 10.2.4.11 provides the baseline demographic characteristics of patients in the van Oosterhout et al (2005) study, which assessed the use of d4T/3TC/NVP in HIV patients in Malawi. A total of 717 patients were eligible for the study, however 453 did not attend the clinic for a planned visit. Of the 264 patients who started treatment, 88 did not meet the entry criteria for the study, leaving 176 patients enrolled in the study.

Table 10.2.4.11: Baseline demographic characteristics of the van Oosterhout et al (2005) study

Characteristic	d4T/3TC/NVP (n=176)
Age groups (number (%))	
18-29	19 (11%)
30-39	70 (40%)
40-49	54 (31%)
≥50	33 (19%)
Gender (% male)	45%
WHO stage (number (%))	
I	7 (4%)
II	40 (23%)
III	56 (32%)
IV	22 (12%)
unknown	51 (29%)
CD4 strata cells/mm3 (number (%))	
<100	46 (26%)
100-199	49 (28%)
200-349	47 (27%)
>350	17 (10%)
unknown	17 (10%)

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

Table 10.2.4.12 provides the results of the van Oosterhout et al (2005) study.

Table 10.2.4.12: Results of van Oosterhout et al (2005)

Outcome	Results
WHO Stage IV event or pulmonary tuberculosis	•12 patients
Viral load	•20% had detectable viral load
CD4 count	•mean increase of 68 cells/mm3 (95% CI: 36, 99) •56% had increase >25% per year •9% had increase <25% •34% had decrease
Treatment adherence	•52% reported never missing a tablet •reason for missing dose: unavailability of drug in hospital pharmacy (43%); financial constraints (32%); forgetting to take tablet (27%)

The authors conclude that the large number of patients who visited the clinic but did not return was most likely related to drug costs. For those patients who did initiate treatment, the results showed good virological and clinical outcomes.

10.3 Summary of available estimates of comparative effectiveness

The results of the systematic review (Siegfried et al., 2006) assessing the comparative effectiveness of d4T/3TC/NVP and other available treatment regimens (ie d4T/3TC/EFZ, AZT//3TC/NVP, d4T/ddl/NVP) show that it has similar efficacy to other treatment regimens, based on changes in viral load and CD4 counts. These surrogate outcome measures are widely accepted as valid.

The results of the non-randomised studies, all assessing the use of d4T/3TC/NVP in resource-poor settings, provide evidence of the efficacy of this ARV regimen across a number of patient groups. Changes to viral load measures and CD4 counts are similar to what have been seen in randomised trials and cohort studies performed in developed countries, but clinical event rates and in particular mortality have been higher in the resource poor settings. This suggests that patients are commencing treatment at a more advanced stage in their illness and co-morbidities, in particular opportunistic and intercurrent infections, are more frequent at baseline. Also, diagnostic and treatment facilities are lacking. The data reviewed here, and the comments of the researchers, indicate that these factors are the most important determinants of the poorer clinical outcomes, rather than poor adherence, viral resistance or inferior quality of the drugs themselves.

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 significant proportion of these are using fixed dose combinations, including d4T, 3TC and NVP.

11.2 Description of adverse effects/reactions

Table 11.2.1 provides a summary of adverse events reported in the Siegfried et al (2006) systematic review for the French et al (2002) trial.

Table 11.2.1: Adverse event results in the French et al (2002) trial as reported in the Siegfried et al (2006) systematic review)

Adverse event	d4T/3TC/NVP	AZT/3TC/NVP	D4T/ddI/NVP
Grade 3 or 4 events	8/22	4/30	7/23
Drug-related Grade 3 or 4 events	5/8	4/4	5/7
Cease treatment due to serious AEs	4/22	3/30	3/23

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

Five of the adverse events leading to treatment discontinuation were due to neuropathy, developing at or after week 12, with 3 in patients treated with d4T/3TC backbone and 2 in patients treated with d4T/ddI backbone. One patient in each treatment group ceased treatment due to development of rash, with cessation definitely attributed to nevirapine in one of these patients.

Table 11.2.2 presents a summary of adverse events and laboratory toxicity in the van Leth et al (2004) trial.

Table 11.2.2: Adverse events and laboratory toxicity in the van Leth et al 92004) trial

	d4T/3TC/bd and NVP/od (n=220)	d4T/3TC/NVP bd (n=387)	d4T/3TC/bd and EFZ/od (n=400)	d4T/3TC/bd NVP/EFZ od (n=209)
Grade 3 or 4 adverse event				
Total number of with event	33 (15.0%)	79 (20.4%)	72 (18.0%)	51 (24.4%)
Hepatobiliary	4 (1.8%)	10 (2.6%)	2 (0.5%)	2 (1.0%)
Clinical hepatitis	3 (1.4%)	8 (2.1%)	1 (0.3%)	2 (1.0%)
Cutaneous	9 (4.1%)	14 (3.6%)	15 (3.8%)	12 (5.7%)
Rash	9 (4.1%)	13 (3.4%)	8 (2.0%)	11 (5.3%)
CNS/psychiatric	3 (1.4%)	14 (3.6%)	22 (5.5%)	16 (7.7%)
Insomnia/abnormal dreams	0	0	6 (1.5%)	5 (2.4%)
Anxiety	0	0	4 (1.0%)	3 (1.4%)
Depression	0	1 (0.3%)	6 (1.5%)	1 (0.5%)
Diarrhoea	1 (0.5%)	3 (0.8%)	4 (1.0%)	4 (1.9%)
Vomiting	3 (1.4%)	4 (1.0%)	4 (1.0%)	3 (1.4%)
Pyrexia	2 (0.9%)	8 (2.1%)	3 (0.8%)	2 (1.0%)
Adverse events leading to temporary or permanent discontinuation of treatment				
Rash	27 (12.3%)	25 (6.5%)	15 (3.8%)	29 (13.9%)
CNS/psychiatric	11 (5.0%)	22 (5.7%)	27 (6.7%)	16 (7.7%)
Clinical hepatitis	4 (1.8%)	6 (1.6%)	1 (0.3%)	2 (1.0%)
Peripheral neuropathy	6 (2.7%)	12 (3.1%)	9 (2.3%)	8 (3.8%)
Hepatic laboratory abnormality	13 (5.9%)	9 (2.3%)	1 (0.3%)	6 (2.9%)
Vomiting	1 (0.5%)	5 (1.3%)	5 (1.3%)	4 (1.9%)
Laboratory toxicities				
Hepatobiliary	30 (13.6%)	32 (8.3%)	18 (4.5%)	19 (9.1%)
Non-hepatobiliary	20 (9.1%)	53 (13.7%)	41 (10.3%)	22 (10.5%)
Neutropenia	6 (2.7%)	17 (3.9%)	9 (2.3%)	13 (6.2%)
Amylase increased	4 (1.8%)	13 (3.6%)	15 (3.8%)	3 (1.4%)
Triglycerides increased	3 (1.4%)	5 (1.3%)	5 (1.3%)	1 (0.5%)
Alkaline phosphatase	2 (0.9%)	5 (1.3%)	3 (0.8%)	4 (1.9%)

3TC=lamivudine; d4T=stavudine; NVP=nevirapine; EFZ=efavirenz; bd=twice daily; od=once daily

A statistically significantly greater number of patients treated with d4T/3TC twice daily combined with NVP and EFZ once daily experienced a Grade 3 or 4 adverse event compared to those treated with d4T/3TC twice daily combined with NVP once daily (p=0.014). There was a statistically significantly greater occurrence of hepatobiliary laboratory toxicities in patients treated with d4T/3TC twice daily combined with NVP once daily compared to those treated with NVP twice daily (p=0.036), while those treated with d4T/3TC/NVP twice daily had a statistically significantly greater occurrence of hepatobiliary toxicities compared to those treated with d4T/3TC twice daily combined with EFZ once daily (p=0.030).

One patient treated with twice daily NVP developed fulminant hepatitis, attributed to the use of nevirapine, as well as pancreatitis and renal failure. Another patient treated with NVP twice daily developed Stevens-Johnson syndrome, attributed to the use of nevirapine. One patient treated with NVP once daily died of lactic acidosis attributed to the use of d4T.

Table 11.2.3 summarises the occurrence of adverse events in the non-randomised studies.

Table 11.2.3: Summary of adverse events in non-randomised studies

Study	Adverse events
Calmy et al., 2006	•AEs reported only for a subset (n=655) after 12 months therapy •treatment discontinued due to nevirapine toxicity in 42 patients, with 15 due to tuberculosis, 12 due to skin toxicity, 11 due to liver toxicity and 4 for unknown reasons. •treatment discontinued due to stavudine toxicity in 9 patients, with 5 due to neuropathy, 2 due to lipodystrophy and 2 for unknown reasons.
Pujari et al., 2004	•rash reported in 6.6% of patients •clinical hepatitis reported in 3.2% of patients •gastrointestinal disturbances (eg vomiting, nausea) in 15.5% of patients •8 patients developed a Grade 4 rash, and 2 died •most rashes occurred when a patient switched from lead-in dose to full dose •female gender associated with higher risk of development of AE (OR=0.5; 95% CI: 0.3, 0.8; p=0.02)
Idigbe et al., 2005	•26 patients (52%) reported no adverse events •18 patients (36%) reported Grade 1 to 2 events •2 patients (4%) developed active pulmonary tuberculosis
Laurent et al., 2004	•5 Grade 3 events were attributed to study treatment (incidence 17.8/100 person-years; 95% CI: 7.4, 42.7) •one patient developed generalised uticaria and had raised alanine aminotransferase, both disorders resolved when nevirapine was replaced with indinavir •two patients had increased alanine aminotransferase and one patient had transient amylase rise, study treatment not discontinued in these 3 patients •3 cases of Grade 1 and 1 case of Grade 2 peripheral neuropathy reported •no Grade 4 events reported
Anekthananon et al., 2004	•12% of patients developed skin rashes •Grade 3 or 4 hepatotoxicity reported in 7% of patients
Tin et al., 2005	•16.8% of patients had symptoms of lipodystrophy within 2 years of treatment •statistically significant association between older age (40-49) and occurrence of lipodystrophy (p=0.043)
van Oosterhout et al., 2005	•76% of patients experienced at least one AE •most common AE was numbness and/or pain of lower extremities (56%) •rash reported by 26% of patients •no patients had rise in transaminase more than 5 times the upper limit of normal

A retrospective case review by Subsai et al (2006)[14] assessed the occurrence of neurological immune restoration inflammatory syndrome (NIRIS) in patients in Thailand treated with d4T/3TC/NVP compared to the patients prior to availability of this treatment regimen. The review found that the incidence rates of NIRIS, such as progressive multifocal leukoencephalopathy (PML), cerebral toxoplasmosis and cytomegalovirus retinitis were lower than the previous incidence in patients who had not received HAART treatment. However, the incidence rates of non-NIRIS events such as ischaemic stroke, haemorrhagic stroke and primary central nervous system lymphoma increased following the introduction of d4T/3TC/NVP regimen in Thailand (p=0.001).

An assessment of hepatotoxicity associated with nevirapine was conducted by Sanne et al (2005)[15]. In this study, 468 South African HIV patients received either 3TC or emtricitabine, d4T and either NVP or EFZ. Regression analysis as used to identify risk factors for hepatotoxicity. The

study found an occurrence of early hepatotoxicity of 17% in the NVP group and 0% in the EFZ group, balanced between the 3TC and emtricitabine arms. The identified independent risk factors were BMI <18.5, female gender, serum albumin level <35 g/L, mean corpuscular volume >85 fL, HIV RNA <20,000 copies/mL, aspartate aminotransferase level <75 IU/L and lactate dehydrogenase level <164 IU/L. The authors concluded that the use of NVP in female patients with a low BMI should be discouraged.

A cross-sectional study by Pujari et al (2005)[16] assessing lipodystrophy and dyslipidaemia in patients taking d4T/3TC/NVP or AZT/3TC/NVP documented lipoatrophy in 26.7% of patients on d4T/3TC/NVP and lipohypertrophy in 23.3% of patients taking d4T/3TC/NVP.

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

As noted above a low BMI may be associated with increased hepatic toxicity with nevirapine.

11.4 Summary of comparative safety against comparators

Based on the van Leth et al (2004), there was a greater occurrence of adverse events, in particular hepatobiliary toxicities, associated with NVP treatment compared to EFZ treatment. The study by Sanne et al (2005) reported a greater occurrence of hepatotoxicity in patients treated with NVP (17%) compared to those treated with EFZ (0%). NVP was also associated with occurrence of fulminant hepatitis in one patient and Stevens-Johnson syndrome in one patient in the van Leth et al (2004) trial. However rates of CNS side effects were higher with Efavirenz and it cannot be used in pregnancy.

The WHO Guidelines[3] state that a higher incidence of rash is associated with NVP compared to EFZ, and NVP 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 NVP 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/mm3.

In the van Leth et al (2004) trial, one patients died of lactic acidosis attributed to the use of d4T. As the available trials included d4T in the comparator arms, it is not possible to assess adverse events attributable solely to the use of d4T. However, the WHO Guidelines state that d4T is the NRTI most associated with lactic acidosis, lipoatrophy and peripheral neuropathy. The guidelines state that it is important to begin planning to move away from d4t-containing regimens so as to avoid or minimise the predictable toxicities associated with the drug. However, as d4T is the most accessible option for many patients, the Guidelines recommend enhanced and close monitoring for short- and long-term d4T toxicities.

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 price of d4T/3TC/NVP ranges from $0.08 (Honduras) to $12.45 per unit (Rwanda), with annual treatment costs ranging from $59 to $9,089 per patient per year. The unit cost in most countries was around $0.20 and the weighted average price of d4T/3TC/NVP in 2005 in low income countries was $USD144 per patient per year, while the weighted average cost in middle income countries was $USD365 per patient per year.

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 HART lay between $US 1100 and 1800.[17] Any value like this will be sensitive to the costs that were included in the model and the prices paid for ARV therapy. A judgement about cost-effectiveness is very context specific and will depend heavily on the perspective of the payer. A more recent study from the University of Capetown in South Africa (Cleary et al 2004. http://www.hst.org.za/uploads/files/arv_cost.pdf)[18] used a Markov model to simulate the outcomes and costs of introducing ARV therapy into a South African township. The study included a wide range of direct costs, but no productivity gains resulting from effective treatment. The treatment scenarios used in this study included a fixed dose combination product containing 3TC d4T and NVP, and also included the use of alternative non-nucleoside transferase inhibitors and other second line drugs, which are more expensive. This study included a range of direct costs, including anti-retroviral drugs at an average annual purchase cost of 4000 to 5000 Rand ($US 550 – 700), which is higher than the international prices for a FDC product containing 3TC d4T and NVP. The overall cost-effectivenes 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 lower, particularly if productivity gains were included.

13. Regulatory status

Table 13.1 provides the regulatory status of d4T/3TC/NVP as recorded in the WHO drugs database (2005)[17]. 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 d4T/3TC/NVP has been registered and the information confirmed by the national drug regulatory authority include Kenya, Malaysia and India. Two generic brands of d4T/3TC/NVP have also been pre-qualified by the WHO (http://mednet3.who.int/prequal/).

Table 13.1 – Regulatory status as based on WHO drugs database

INN and dosage	Manufacturer and country	Countries that have granted registration
Lamivudine 150mg + stavudine 30mg + nevirapine 200mg, FDC tablet	Ranbaxy Ltd, India	*WHO prequalified*, Benin, India, Ivory Coast, Kenya, Madagascar, Malawi, Tanzania
	Cosmos Pharmaceutical Ltd, Kenya	Kenya
	Hetero Drugs, India	Burundi, Congo, India, Kenya, Malawi, Nigeria, Zambia
	Cambodia Pharmaceutical Enterprise	Cambodia
	Government Pharmaceutical Organization, Thailand	Cambodia, Thailand
	Cipla, India	*WHO prequalified*, Benin, Cambodia, Chad, Congo, Gabon, Gambia, Guinea, Malawi, Mali, Mauritania, Myanmar, Sierra Leone, Sudan, Tanzania, Togo, Uganda, Ukraine
	Strides Arcolab Ltd, India	Burkina Faso, Chad, India, Kenya, Malawi, Nigeria, Uganda
	Duopharma, Malaysia	Malaysia
	Aurobindo	India
	Emcure, India	India
Lamivudine 150mg + stavudine 40mg + nevirapine 200mg, FDC tablet	Ranbaxy Ltd, India	*WHO prequalified*, Benin, Gabon, India, Ivory Coast, Kenya, Madagascar, Malawi, Nigeria, Tanzania
	Cambodia Pharmaceutical Enterprise	Cambodia
	Eastern Surgical Company, India	India
	Hetero Drugs, India	Burundi, Congo, India, Kenya, Malawi, Nigeria, Uganda, Zambia
	Government Pharmaceutical Organization, Thailand	Cambodia, Thailand
	Strides Arcolab Ltd, India	Burkina Faso, Chad, India, Kenya, Malawi, Nigeria, Uganda
	Duopharma, Malaysia	Malaysia
	Aurobindo	India
	Cipla, India	*WHO prequalified*, Benin, Cambodia, Chad, Congo, Gabon, Gambia, Guinea, Malawi, Mali, Mauritania, Myanmar, Sierra Leone, Sudan, Tanzania, Togo, Uganda, Ukraine
	Emcure, India	India

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

14. Availability of pharmacopoeial standards

The individual components that comprise the d4T/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 recently 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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