VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

HIV infection: [2] There are approximately 34 million people currently living with HIV and nearly 30 million people have died of AIDS-related causes since the beginning of the epidemic.[3, 4, 5] While cases have been reported in all regions of the world, almost all those living with HIV (97%) reside in low- and middle-income countries, particularly in sub-Saharan Africa.HIV primarily affects those in their most productive years; about half of new infections are among those under age 25. [6]

HIV has led to a resurgence of tuberculosis (TB), particularly in Africa, and TB is a leading cause of death for people with HIV worldwide.[7, 8]Women represent about half of all people living with HIV worldwide, and more than half (58%) in sub-Saharan Africa. HIV is the leading cause of death among women of reproductive age. Gender inequalities, differential access to services, and sexual violence increase women's vulnerability to HIV, and women, especially younger women, are biologically more susceptible to HIV. Globally, there were 3.3 million children living with HIV in 2011, 330,000 new infections among children (a decrease of 24% from 2009-2011), 230,000 AIDS deaths, and approximately 17.3 million AIDS orphans (children who have lost one or both parents to HIV), most of whom live in sub-Saharan Africa (88%).

VI.2.2 Summary of treatment benefits

Treatment regimens of HIV-infected patients

Regimens designated as "preferred" are supported by clinical trial data that suggest optimal efficacy and durability, favorable tolerability and toxicity profile, and ease of use in treatment-naive patients. "Alternative regimens" are also effective and tolerable, but have potential disadvantages when compared to preferred regimens. Based on individual patient characteristics, a regimen listed as alternative may be the preferred regimen for a particular patient. Regimens designated as "acceptable" have less virologic activity, lack efficacy data from large clinical

trials, have more toxicities, requires additional testing, pill burden, or drug interaction potential compared with preferred or alternative regimens.

Preferred regimens

- ***Preferred regimens (nonpregnant patients):***
  - Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI)-based regimen:
    - Efavirenz* plus *tenofovir* plus emtricitabine (lamivudine may be used instead of emtricitabine) (AI)

      *except in first trimester of pregnancy or in women with high pregnancy potential
  - Protease Inhibitor-based regimen:
    - Atazanavir* plus ritonavir plus *tenofovir* plus emtricitabine (lamivudine may be used instead of emtricitabine) (AI); OR
    - Darunavir plus ritonavir (once daily) plus *tenofovir* plus emtricitabine (lamivudine may be used instead of emtricitabine) (AI)

      *do not use atazanavir plus ritonavir in patients requiring greater than 20 mg/day of omeprazole equivalent
  - Integrase strand transfer inhibitor-based regimen:
    - Raltegravir plus *tenofovir* plus emtricitabine (lamivudine may be used instead of emtricitabine) (AI)
- ***Preferred regimen (pregnant women):***
    - Lopinavir plus ritonavir (twice-daily) plus zidovudine plus lamivudine (emtricitabine may be used instead of lamivudine) (AI)

Nevirapine plus either *tenofovir* or zidovudine plus either lamivudine or emtricitabine is an acceptable NNRTI-based regimen in treatment-naive, HIV-infected adults and adolescents.[9]

VI.2.3 Unknowns relating to treatment benefits

Renal impairment: the pharmacokinetics of efavirenz have not been studied in patients with renal insufficiency; however, less than 1% of an efavirenz dose is excreted unchanged in the urine, so the impact of renal impairment on efavirenz elimination should be minimal. There is no experience in patients with severe renal failure and close safety monitoring is recommended in this population.

Elderly patients: insufficient numbers of elderly patients have been evaluated in clinical studies to determine whether they respond differently than younger patients.

Hepatic impairment: efavirenz is not recommended in patients with moderate hepatic impairment because of insufficient data to determine whether dose adjustment is necessary. Because of the extensive cytochrome P450-mediated metabolism of efavirenz and limited clinical experience in patients with chronic liver disease, caution must be exercised in administering efavirenz to patients with mild hepatic impairment. The safety and efficacy of efavirenz has not been established in patients with significant underlying liver disorders.

Paediatric population: Efavirenz has not been evaluated in children below 3 years of age or who weigh less than 13 kg. Therefore, efavirenz should not be given to children less than 3 years of age.

Efavirenz plasma exposure may be increased in *patients with the homozygous G516T genetic variant of the CYP2B6 isoenzyme*. The clinical implications of such an association are unknown; however, the potential for an increased frequency and severity of efavirenz-associated adverse events cannot be excluded.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Psychiatric adverse reactions and nervous system symptoms (Psychiatric adverse reactions and nervous system	*Psychiatric symptoms* have been reported in patients treated with efavirenz. The symptoms include severe	Patients should be advised to contact their doctor immediately if they experience psychiatric

Risk	What is known	Preventability
symptoms)	depression, death by suicide, delusions and psychosis-like behaviour. *Nervous system symptoms* usually begin during the first one or two days of therapy and generally resolve after the first 2-4 weeks. The symptoms include dizziness, insomnia, somnolence, impaired concentration and abnormal dreaming. *Seizures:* convulsions have been observed in patients receiving efavirenz, generally in the presence of known medical history of seizures.	symptoms. Caution is advised in patient with history of seizure. Patients with hepatic impairment should be monitored carefully for dose related adverse reaction especially nervous system symptoms. Follow the appropriate dosing time and method of administration (on an empty stomach, bedtime dosing)
Skin rash and severe skin reactions (Skin rash and severe skin reactions)	Mild to moderate rash has been reported in clinical studies with efavirenz and usually resolves with continued therapy. Severe rash associated with blistering, moist desquamation or ulceration has been reported in less than 1% of patients treated with efavirenz. The	Follow the appropriate method of administration (on an empty stomach) Appropriate antihistamines and/or corticosteroids may improve the tolerability and hasten the resolution of rash, they can be used also as prophylaxis in paediatric patients prior to initiating

Risk	What is known	Preventability
	incidence of erythema multiforme or Stevens-Johnson syndrome was approximately 0.1%. Efavirenz must be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement or fever.	therapy with efavirenz.
High-grade hepatic enzyme elevation and severe hepatic events	Patients (even without pre-existing hepatic disease or other risk factors) treated with efavirenz may be at increased risk of developing hepatic failure. Patients with chronic hepatitis B or C and treated with combination antiretroviral agents have a higher risk for severe and potentially life-threatening liver problems.	Patients with mild liver disease may be treated with their normally recommended dose of efavirenz Liver enzyme monitoring should be considered for patients without pre-existing hepatic dysfunction or other risk factors. Before using efavirenz, tell your doctor if you have problems with your liver or have hepatitis. Your doctor may want to do tests to check your liver while you take efavirenz or

Risk	What is known	Preventability
		may switch you to another medicine.
Fetal neural tube abnormalities (including m meningomyelocele, spina bifida, or hydrocephalus) associated with first trimester exposure to EFV	Pregnant women treated with efavirenz especially during the first trimester may be at increased risk, that their baby develops a neural tube defect. All together there have been six retrospective reports of findings consistent with neural tube defects in mothers exposed to efavirenz in the first trimester. A causal relationship of these events to the use of efavirenz has not been established.	Efavirenz should not be used during pregnancy, unless the patient's clinical condition requires such treatment. Women of childbearing potential should undergo pregnancy testing before initiation of efavirenz. Patients should be advised to tell your doctor right away if you are pregnant. Also talk with your doctor if you want to become pregnant.
Alteration in blood levels and CYP2B6 generic polymorphism	Efavirenz plasma exposure may be increased in patients with the homozygous G516T genetic variant of the CYP2B6 isoenzyme. The clinical implications of such an association are unknown; however, the potential for an increased frequency and severity of efavirenz-associated adverse events	Coadministration of efavirenz with drugs primarily metabolized by these isoezymes may result in altered plasma concentrations of the coadministered drug. Follow the appropriate dosing time and method of administration (on an empty stomach, bedtime dosing) Patients should be advised to

Risk	What is known	Preventability
	cannot be excluded.	do not take any other medicines without checking with your doctor.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Urolithiasis/Nephrolithiasis	Not Proposed in SmPC
Malignant neoplasms	Not Proposed in SmPC

Important missing information

Risk	What is known
Missing data on use in children younger than 3 years (Use in pediatric populations (< 3 years old))	Efavirenz has not been evaluated in children below 3 years of age or who weigh less than 13 kg. Therefore efavirenz should not be given to children less than 3 years of age.
Missing data on use of efavirenz in elderly patients (Use in in elderly patients)	Insufficient numbers of elderly patients have been evaluated in clinical studies to determine whether they respond differently than younger patients.
Missing data on use of efavirenz in patients with kidney impairment (Patients with renal impairment)	The pharmacokinetics of efavirenz has not been studied in patients with renal insufficiency; however, less than 1% of an efavirenz dose is excreted unchanged in the urine, so the impact of renal impairment on efavirenz

Risk	What is known
	elimination should be minimal. There is no experience in patients with severe renal failure and close safety monitoring is recommended in this population.
Missing data on use of efavirenz in patients with hepatic impairment (Patients with hepatic impairment)	Efavirenz is not recommended in patients with moderate hepatic impairment because of insufficient data to determine whether dose adjustment is necessary. Because of the extensive cytochrome P450-mediated metabolism of efavirenz and limited clinical experience in patients with chronic liver disease, caution must be exercised in administering efavirenz to patients with mild hepatic impairment. The safety and efficacy of efavirenz has not been established in patients with significant underlying liver disorders. Laboratory test should be performed to evaluate patient´s liver disease at periodic intervals.