

2008 HIV/AIDS IMPLEMENTERS' MEETING

**When and What to Start as first-line:
implications for guidelines, cost and
implementation for adults and children**

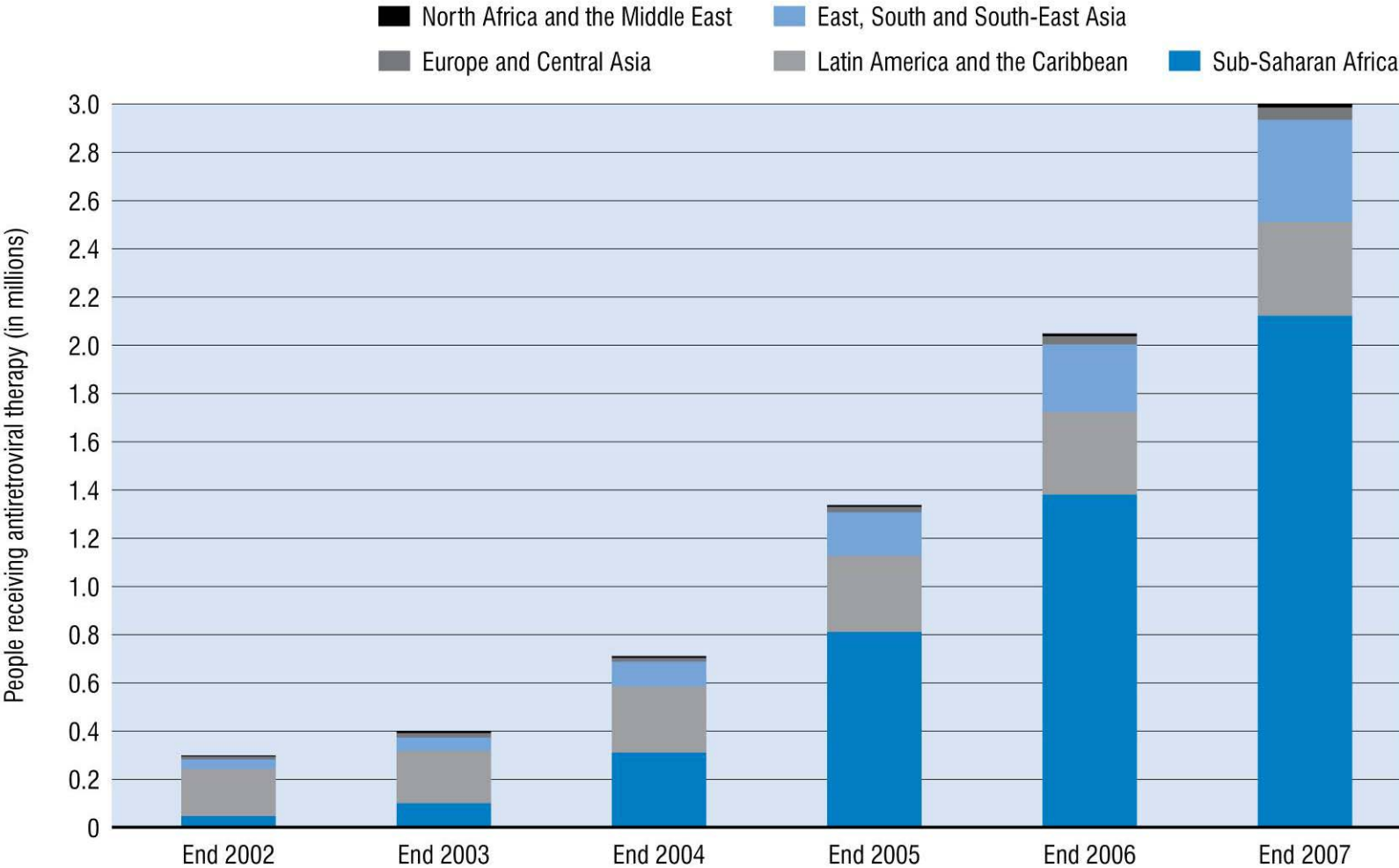
Prof Charlie Gilks

Department HIV/AIDS

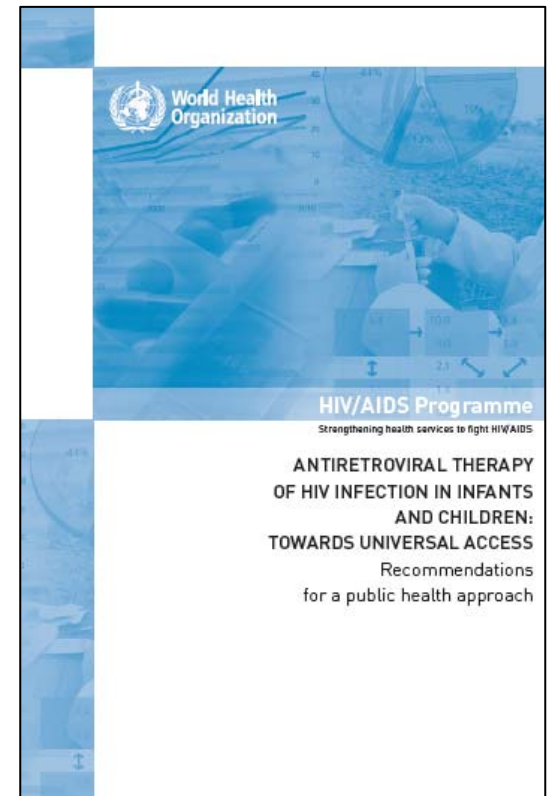
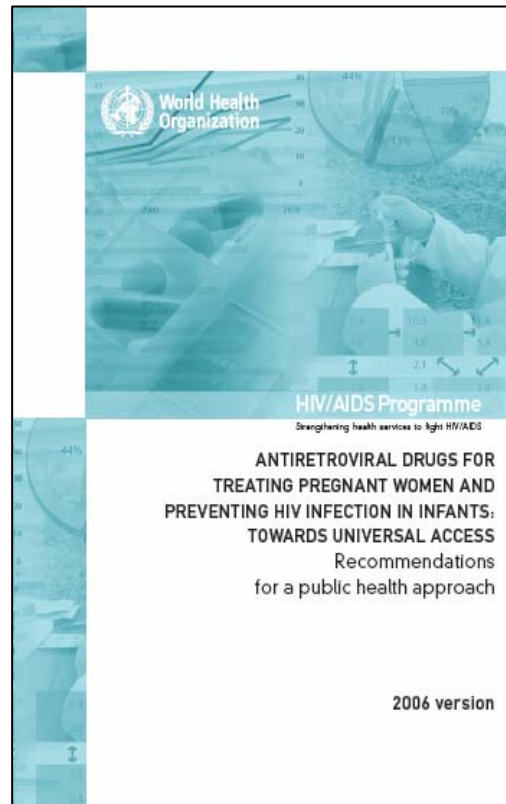
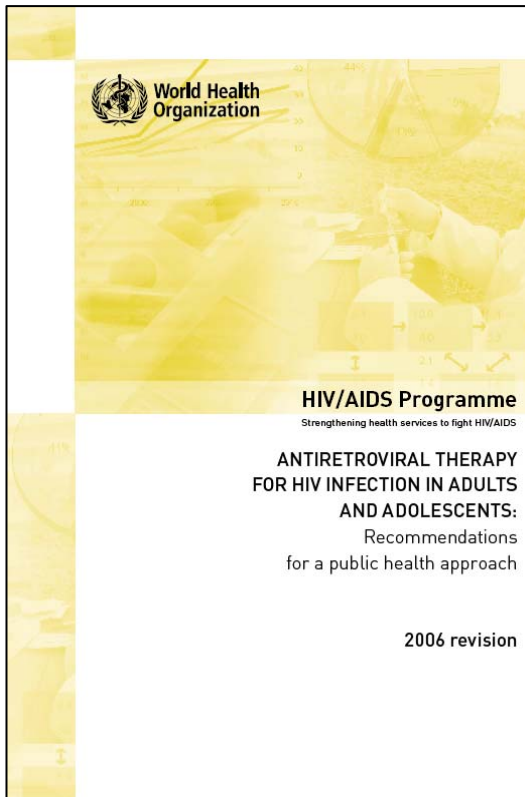
WHO Geneva



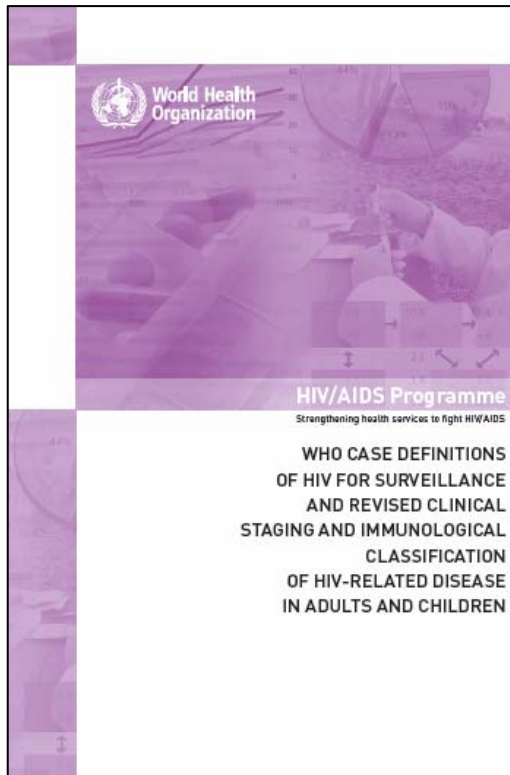
Number of people receiving antiretroviral therapy in low- and middle-income countries, 2002–2007



Harmonised ART Policy Guidance



REVISED WHO CLINICAL STAGING OF HIV FOR ADULTS AND CHILDREN (2006)



PRIMARY HIV INFECTION
Unrecognized Acute retroviral syndrome
CLINICAL STAGE 1
Asymptomatic Persistent generalized lymphadenopathy (PGL)
CLINICAL STAGE 2
Moderate unexplained weight loss (<10% of presumed or measured body weight) Recurrent upper respiratory tract infections (sinusitis, bronchitis, otitis media, pharyngitis) Herpes zoster Angular cheilitis Recurrent oral ulcerations Papular pruritic eruptions Seborrhoeic dermatitis Fungal nail infections of fingers
CLINICAL STAGE 3
<i>Conditions where a presumptive diagnosis can be made using clinical signs or simple investigations</i> Severe weight loss ($\geq 10\%$ presumed or measured body weight) Unexplained chronic diarrhoea for longer than one month Unexplained persistent fever (intermittent or constant for longer than 1 month) Oral candidiasis Oral hairy leukoplakia Pulmonary tuberculosis (diagnosed in last two years) Severe presumed bacterial infections (e.g. pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteremia) Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis
<i>Conditions where confirmatory diagnostic testing is necessary</i> Unexplained Anaemia ($< 8 \text{ gm/dl}$), neutropenia ($< 1,000/\text{mm}^3$) or thrombocytopenia ($< 50,000/\text{mm}^3$) for more than 1 month
CLINICAL STAGE 4
<i>Conditions where a presumptive diagnosis can be made using clinical signs or simple investigations:</i> HIV wasting syndrome Pneumocystis pneumonia Recurrent severe or radiological bacterial pneumonia Chronic Herpes simplex infection; (orolabial, genital, or anorectal of more than 1 month duration, or visceral any duration) Oesophageal Candidiasis Extrapulmonary tuberculosis Kaposi's sarcoma CNS toxoplasmosis HIV encephalopathy
<i>Conditions where confirmatory diagnostic testing is necessary:</i> Extrapulmonary Cryptococcosis including meningitis Disseminated non-tuberculous mycobacteria infection Progressive multifocal leukoencephalopathy (PML) Candida of trachea, bronchi, or lungs Cryptosporidiosis Isosporiasis Cytomegalovirus infection (retinitis or of an organ other than liver, spleen, or lymph nodes) Any disseminated mycosis (e.g. Histoplasmosis, Coccidiomycosis, Penicilliosis) Recurrent non-typhoidal salmonella septicaemia Lymphoma (Cerebral or B cell non-Hodgkin's) Invasive cervical carcinoma Visceral Leishmaniasis
CLINICAL STAGE ON ART

STAGE 1
Asymptomatic Persistent generalized lymphadenopathy (PGL) Hepatosplenomegaly
STAGE 2
Recurrent or chronic upper respiratory tract infections (otitis media, otitis externa, sinusitis) Papular pruritic eruptions Seborrhoeic dermatitis Extensive Human papilloma virus infection Extensive Molluscum infection Herpes zoster Fungal nail infections Recurrent oral ulcerations Linear Gingival Erythema (LGE) Angular cheilitis Parotid enlargement
STAGE 3
<i>Conditions where a presumptive diagnosis can be made using clinical signs or simple investigations</i> Unexplained moderate malnutrition not adequately responding to standard therapy Unexplained persistent diarrhoea (14 days or more) Unexplained persistent fever (intermittent or constant, for longer than 1 month) Oral candidiasis (outside neonatal period) Oral hairy leukoplakia Acute necrotizing ulcerative gingivitis/periodontitis Pulmonary tuberculosis Severe recurrent presumed bacterial pneumonia
<i>Conditions where confirmatory diagnostic testing is necessary</i> Lymphoid interstitial pneumonia (LIP) Unexplained Anaemia ($< 8 \text{ gm/dl}$), neutropenia ($< 1,000/\text{mm}^3$) or thrombocytopenia ($< 50,000/\text{mm}^3$) for more than 1 month Chronic HIV associated lung disease including bronchiectasis
STAGE 4
<i>Conditions where a presumptive diagnosis can be made using clinical signs or simple investigations:</i> Unexplained severe wasting or severe malnutrition not adequately responding to standard therapy Pneumocystis pneumonia Recurrent severe presumed bacterial infections (e.g. empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia) Chronic Herpes simplex infection; (orolabial or cutaneous of more 1 month duration, visceral of any duration) Extrapulmonary tuberculosis Kaposi's sarcoma Oesophageal Candidiasis CNS Toxoplasmosis (outside the neonatal period) HIV encephalopathy
<i>Conditions where confirmatory diagnostic testing is necessary:</i> CMV infection (CMV retinitis or infection of organ other than liver, spleen, or lymph nodes onset at age 1 month or more) Cryptococcal meningitis (or other extrapulmonary disease) Any disseminated endemic mycosis (e.g. extra-pulmonary Histoplasmosis, Coccidiomycosis, Penicilliosis) Cryptosporidiosis Isosporiasis Disseminated non-tuberculous mycobacteria infection Candida of trachea, bronchi or lungs Acquired HIV related rectal fistula Cerebral or B cell non-Hodgkin's Lymphoma Progressive multifocal leukoencephalopathy (PML) HIV related cardiomyopathy or HIV related nephropathy
STAGE ON ART

Immunological classification- all ages

HIV associated immunodeficiency	Age related CD4 (%CD4+ or absolute count)			
	<11m (%)	12-35m (%)	36-59m (%)	≥5yr (count/%)
Not significant	> 35	>30	>25	<500
Mild	30-35	25-30	20-25	350-499
Advanced	25-29	20-24	15-19	201-349
Severe	<25	<20	<15	<200



When to Start - adults

Table 4 - Recommendations for initiating ART in adults and adolescents based on clinical stage and availability of immunological markers

WHO Clinical Staging	CD4 testing not available	CD4 testing available
1	Do not treat [A-III]	Treat if CD4 cell count < 200/mm ³ [A-III] ^a
2	Do not treat ^b [B-III]	
3	Treat [A-III]	Consider treatment if CD4 cell count < 350/mm ³ ^{a c} and initiate ART before CD4 cell count drops below 200/mm ³ ^d [B-III]
4	Treat [A-III]	Treat irrespective of CD4 cell count [A-III]

^a CD4 cell count advisable to assist with determining need for immediate therapy for situations as pulmonary TB and severe bacterial infections, which may occur at any CD4 level.

^b A total lymphocyte count of $\leq 1,200/\text{mm}^3$ can be substituted for the CD4 count when the latter is unavailable and mild HIV disease exist. It is not useful in the asymptomatic patients. Thus, in the absence of CD4 cell count and TLC, patients with WHO Adult Clinical Stage 2 should not be treated.

^c Initiation of ART is recommended in all HIV-infected pregnant women with WHO Clinical Stage 3 disease and CD4 < 350 cells/mm³.

^d The precise CD4 cell level above 200/mm³ at which ARV treatment should be started has not been established.

When to start ART – infants & children

	<12 months	≥12 months
Stage 4	All	All
Stage 3	All	All except TB/LIP/OHL and Thrombocytopenia consider CD4%
Stage 2	All	CD4 guided
Stage 1	All	CD4 guided

Issues for when to start ART with current guidelines

- *Access to CD4 counts / results*
 - Feasibility of decentralised CD4 based strategy
- *Treatment slots and capacity to enroll*
 - National coverage and satisfying demand
- *Estimates for disease burden risen > 30%*
- *Very limited ART initiation in PMTC*

Issues for when to start: earlier initiation of ART at CD4 < 350

- Cohort data not RCTs; all data from industrialised settings
- Costs and feasibility: from 200 to 350 CD4; 10%-30% more will be eligible
- Countries report on coverage ...
- NVP contraindicated in women CD4 > 250
- **But this may impact on HIV transmission**

Issues for when to start ART changing recommendations for pregnant women

- *Treat all pregnant women with cART*
- *Treat all women who are breast-feeding*
 - ? Safe to stop post-partum: SMART data
 - Feasibility in antenatal clinic settings
 - What to use – NVP contraindicated
Loose second-line with PIs; 3NRTIs?
CD4-based strategy ...
 - Harmonised, uniform recommendations

1st and 2nd line ARVs for adults

1st Line

2nd line

Start

Substitute

Switch

Stop

AZT, d4T,
3TC,

NVP; EFV

ABC,
TDF

ddI

PI/r

Recommended 1st Line
ARV Drugs

Frequently
Recommended as 2nd
line drugs, but also as
alternative drugs in 1st
line regimens

Recommended as 2nd Line
Drugs

Preferred first-line / initial ART

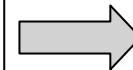
ZDV or d4T + 3TC or FTC + NVP or EFV



Second-line*

ddI + ABC + PI/r

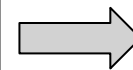
ABC + 3TC or FTC + NVP or EFV



ddI + ZDV + PI/r

NVP-exposed infants

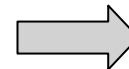
LPV / r + ZDV or d4T + 3TC or FTC



??

Triple NRTI alternative

ZDV or d4T + 3TC or FTC + ABC



NVP or EFV + PI/r

* 3TC can be maintained in a second line regimen

Prioritization of Preferred Options for adult second-line ART

1st Line NRTI Choice	NRTI Component	PI Component
If AZT or d4T is used in 1st line	ABC+ddl TDF+3TC (FTC)	ATV/r LPV/r
If TDF is used in 1st line	AZT+3TC	
If ABC is used in 1st line	AZT+3TC TDF+3TC (FTC)	

Moving the agenda forward: what first-line ARVs to use / not to use

- *Continued use of d4T (including 40mg)*
- *Non-thymidine analogues: TDF/ABC*
- *One pill once a day – Atripla*
 - Relative lack of data on toxicity from RLS
 - ABC hypersensitivity less in Africa (B5701*)
 - Renal screen prior to initiation of TDF
 - TDF not for children and adolescents;
 - ? TDF in pregnancy / breast feeding
 - Costs: TDF/FTC/EFV x 4 ; AC x3 more costly
 - Reduced d4T toxicity costs offset TDF costs 20%

(Sanne CROI 2008 poster 989)

Conclusions

- Guideline development is challenging
- Balance between
 - being permissive; driving ART agenda forward
 - maintaining relevance to countries
 - equity of access across those in need
- Processes updated in WHO (GRADE)
 - Costs and feasibility