



Published in final edited form as:

*HIV Ther.* 2009 September 1; 3(5): 501–526.

## Adult combination antiretroviral therapy in sub-Saharan Africa: lessons from Botswana and future challenges

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### Abstract

Numerous national public initiatives offering first-line combination antiretroviral therapy (cART) for HIV infection have commenced in sub-Saharan Africa since 2002. Presently, 2.1 million of an estimated seven million Africans in need of cART are receiving treatment. Analyses from the region report favorable clinical/treatment outcomes and impressive declines in AIDS-related mortality among HIV-1-infected adults and children receiving cART. While immunologic recovery, virologic suppression and cART adherence rates are on par with resource-rich settings, loss to follow-up and high mortality rates, especially within the first 6 months of treatment, remain a significant problem. Over the next decade, cART coverage rates are expected to improve across the region, with attendant increases in healthcare utilization for HIV- and non-HIV-related complications and the need for expanded laboratory and clinical services. Planned and in-progress trials will evaluate the use of cART to prevent primary HIV-1 infection with so-called 'test and treat' expansions of coverage and treatment. Education and training programs as well as patient-retention strategies will need to be strengthened as national cART programs are expanded and more people require lifelong monitoring and care.

### Keywords

adherence; cART; combination antiretroviral therapy; efficacy; HIV/AIDS; mortality/survival; sub-Saharan Africa; tolerability/toxicity

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Financial & competing interests disclosure

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

## Update

### HIV/AIDS in Africa

As of December 2007, there were an estimated 33 million persons (range: 30–36 million) living with HIV-1 worldwide [1]. Globally, the HIV-1 epidemic appears to have stabilized despite staggering rates of new infections (estimated at 2.7 million [range: 2.2–3.2 million]) and deaths (estimated at 2.0 million [range: 1.8–2.3 million]) in the year 2007 alone [1]. An estimated 1.9 million (range: 1.6–2.1 million) people were newly infected with HIV-1 in sub-Saharan Africa in 2007, bringing the regional total 22 million (range: 20.5–23.6 million) persons living with HIV-1, and representing 67% of the global burden [1].

Certain individuals appear to be at a heightened risk for specific medication-related toxicities, many of which are life-threatening. Preliminary evidence suggests the incidence and patterns of genotypic drug-resistance mutations in sub-Saharan Africa differ from western Europe and North America, perhaps due in part to a higher prevalence of HIV-1 subtype C infection. Opportunistic infections and malignancies, especially TB, continue to cause significant morbidity and mortality in sub-Saharan Africa.

The epidemic of HIV-1 infection in sub-Saharan Africa varies significantly from country to country in scale, scope and in dominant circulating HIV-1 subtype [1]. The reported adult national HIV-1 prevalence is less than 2% in many west and central African countries, while in 2007 the prevalence rate exceeded 15% in seven southern African countries (Botswana, Lesotho, Namibia, South Africa, Swaziland, Zambia and Zimbabwe), and was greater than 5% in seven other countries (Cameroon, the Central African Republic, Gabon, Malawi, Mozambique, Uganda and Tanzania) [1]. In Botswana, reductions in HIV-1 prevalence among pregnant 15–19-year-olds (from 25% in 2001 to 18% in 2006) suggest that the rate of new HIV-1 infections is on the decline in that nation [1,2]. The epidemics in Malawi and Zambia also appear to have stabilized, amid some evidence of favorable behavior changes [1,3] and signs of declining HIV-1 prevalence among women presenting for routine antenatal care [1, 4-7]. HIV-1 surveillance data from antenatal clinics in South Africa also suggest that the country's epidemic is stabilizing [1,8], but there is little evidence to date of major behavioral changes among those most 'at-risk' of acquiring HIV-1.

In Rwanda, Kenya, Zimbabwe and Uganda, significant changes in sexual behavior have led to declines in the number of new HIV-1 infections and contributed to the global stabilization of new infection rates among adults aged 15–49 years which began in the late 1990s [1]. These gains, however, have not been consistent within or between regions. Favorable epidemiological and behavioral trends [1] have not been sustained in some countries, and the number of new infections is increasing in several areas, including Mozambique [1]. In Lesotho, Namibia, South Africa and Swaziland, HIV-1 prevalence rates have reached extraordinarily high plateaus [1].

The rate of combination ARV therapy (cART) regimen switching due to treatment failure is expected to increase, but at present there are few second-line, and frequently no third-line, options in most resource-limited settings. Ritonavir-boosted lopinavir is the only widely available generic, coformulated, heat-stable protease inhibitor (PI), and bringing additional agents to market is a priority of international health organizations. Newer ART drug or antiretroviral (ARV) classes such as integrase inhibitors and CCR5 antagonists are difficult to implement in resource-limited settings, and are not expected in generic formulations in the near future. The criteria for clinical and immunologic treatment failure criteria used in many cART programs perform poorly for detecting virologic failure, increasing the risk of treatment resistance. Large clinical trials investigating the use and cost-effectiveness of routine monitoring of HIV-1 plasma HIV-1 RNA in clinical care are in progress in resource-limited

settings. Physician-centered care models are not sustainable in sub-Saharan Africa and escalating manpower constraints will require the evaluation and adoption of novel ‘task-shifting’ approaches to care.

### Combination antiretroviral therapy in Africa

The recent increase in access to cART has been impressive in many African countries. As of December 2007, an estimated 3 million people in low- and middle-income countries were receiving cART [1]. Although this represents only 31% of those in need of treatment, it represents a 45% increase in the total number of patients receiving cART in 2006 [1].

Beginning in 2002, ARV therapy (ART) treatment programs have been rolled out in public-sector health facilities in sub-Saharan Africa. In January 2002, ART became available in Botswana in public-sector health facilities through the national ARV treatment program called Masa (‘new dawn’ in Setswana). The Masa program now provides public ART to more than 115,000 people at more than 32 designated national outpatient treatment sites. This success translates to a current cART coverage rate exceeding 90% of estimated HIV cases, one of the highest in the world. Similar programs have been implemented in other countries supported by the WHO and the President's Emergency Plan for AIDS Relief (PEPFAR). In Namibia, where the cART coverage rate was below 1.0% in 2003, 88% of persons in need of treatment were receiving cART as of 2007 [1]. While Rwanda ranked 161st out of 177 countries in the Human Development Index [1,9] and is still recovering from the 1994 genocide, it has increased its cART coverage rates from 1% in 2003 to almost 71% in 2007 [1]. Such impressive expansion in HIV care delivery was made possible by a 40-fold increase in the number of Rwandan ARV treatment sites during this period [1].

With a few exceptions (Botswana, Namibia, Rwanda and Senegal), the majority of African nations still have less than 50% cART coverage. The sub-Saharan African region, as a whole, however, has made significant strides in increasing access to prevention of mother to child transmission (PMTCT) programs. Five countries (Kenya, Namibia, Rwanda, South Africa and Swaziland) have improved coverage to 50–75% of those in need of services, and one country, Botswana, has achieved over 90% coverage (**Box 1**) [1].

### Current cART recommendations

In resource-rich settings, the current gold-standard first-line ART regimen is a combination of the nucleoside reverse transcriptase inhibitors (NRTIs) tenofovir (TDF) plus emtricitabine (FTC) with the non-NRTI (NNRTI) efavirenz (EFV) [10,201]. Other options include the use of two NRTIs, TDF plus FTC or alternatively abacavir (ABC) plus lamivudine (3TC), given with a ritonavir-boosted PI such as atazanavir/ritonavir (ATV/r), fosamprenavir/ritonavir (FPV/r), darunavir/ritonavir or lopinavir/ritonavir (LPV/r) [201]. In multiple adult head-to-head clinical trials, ART-treated persons receiving EFV with zidovudine (ZDV) plus 3TC, and more recently with TDF plus FTC, have experienced the most favorable virological outcomes [11-13,201].

#### Box 1

Combination antiretroviral therapy coverage rates of qualifying (i.e., those with advanced HIV/AIDS) adults and children in Africa\*

Less than 25% coverage

■ Burundi

- Central African Republic
- Chad
- Democratic Republic of Congo
- Djibouti
- Egypt
- Eritrea
- Gambia
- Ghana
- Guinea–Bissau
- Liberia
- Madagascar
- Mauritania
- Mauritius
- Mozambique
- Sierra Leone
- Somalia
- Sudan
- Zimbabwe

*25–49% coverage*

- Angola
- Benin
- Burkina Faso
- Cameroon
- Côte d'Ivoire
- Equatorial Guinea
- Ethiopia
- Gabon
- Guinea
- Kenya
- Lesotho
- Malawi
- Mali
- Morocco
- Nigeria
- South Africa
- Swaziland
- Uganda
- Tanzania
- Zambia

*50–75% coverage*

- Rwanda
- Senegal

*Greater than 75% coverage*

- Botswana

■ Namibia

Breakdown by quartiles (n = 106).

*Data adapted from [1].*

\* All values are based on need estimates using Joint United Nations Programme on HIV/AIDS/WHO methodology. Includes all countries for which the number of adults and children on antiretroviral therapy was reported for 2007, except countries for which UNAIDS/WHO need estimates are not available, or with need estimates less than 500.

The current standard recommendations for first-line adult ART in sub-Saharan Africa consists of two NRTIs plus one NNRTI [14,202]; with the vast majority of ART-treated adults receiving either stavudine (d4T) and 3TC or ZDV and 3TC with either nevirapine (NVP) or EFV. PIs are primarily reserved for secondline treatment, owing to issues of cost, dosing frequency, drug–drug interactions, potential for long-term side effects and higher pill burden. Persons failing first-line regimens in sub-Saharan Africa are usually switched to a regimen of two NRTIs (at least one of which is new) plus a boosted PI, typically LPV/r [14,202].

## When to start cART

Criteria for cART initiation differ between settings and by national guidelines [14]. For example, the current International AIDS Society USA guidelines for treatment of HIV-1 infection in adults [15,16] recommend that cART should be considered in asymptomatic adults once their CD4<sup>+</sup> cell count declines below 350 cells/mm<sup>3</sup> and initiated in all patients whose CD4<sup>+</sup> cell count values are less than 200 cells/mm<sup>3</sup>. In resourcerich settings, the scientific evidence of advantages of starting earlier cART is growing [17], with the standard-of-care evolving to cART initiation as early as the initial HIV-1 diagnosis. By contrast, the 2002 WHO guidelines, which are still used in some countries, recommend cART only for patients with WHO clinical stage 4 disease or a CD4<sup>+</sup> cell count of less than 200 cells/mm<sup>3</sup>. These recommendations were revised in 2003 and now state that cART should also be initiated in patients with both WHO clinical stage 3 disease and a CD4<sup>+</sup> cell count between 200 and 350 cells/mm<sup>3</sup> [203].

The vast majority of national guidelines currently rely on the identification of WHO clinical stage 3 or 4 for cART initiation criteria, rather than using alternative CDC classification definitions. Please refer to **Box 2** for a detailed list of WHO clinical stages for HIV/AIDS.

Data from adult cART-treated programs in Botswana have shown a significantly increased risk of mortality among persons initiating cART with more advanced immunosuppression. In one such study patients initiating cART with a base-line CD4<sup>+</sup> cell count of less than 50 cells/mm<sup>3</sup> had a 3.2-fold higher mortality rate (p = 0.004) compared with patients with a CD4<sup>+</sup> cell count between 51 and 200 cells/mm<sup>3</sup> at the time of cART initiation [18]. All patients had advanced immunosuppression at the time of cART initiation (n = 153, median CD4<sup>+</sup> cell count: 96, interquartile range [IQR]: 33–165, 31% with CD4<sup>+</sup> cell count <50 cells/mm<sup>3</sup>). At 48 weeks the mean CD4<sup>+</sup> increase was 204 cells/mm<sup>3</sup> and 78.8% had achieved an undetectable plasma HIV-1 RNA level [18].

### Box 2

#### WHO clinical staging

Clinical stage 1: asymptomatic

- Asymptomatic
- Persistent generalized lymphadenopathy

#### Clinical stage 2: moderate disease

- Unexplained moderate weight loss of less than 10% of baseline weight
- Recurrent upper respiratory infections (sinusitis, otitis media, tonsillitis, pharyngitis)
- Mono-dermatomal VZV (shingles)
- Recurrent oral ulceration
- Papular pruritic eruptions/dermatitis
- Seborrheic dermatitis
- Fungal nail infections

#### Clinical stage 3: advanced disease

- Unexplained weight loss above 10% of baseline
- Unexplained chronic diarrhea for more than 1 month
- Unexplained persistent fever (>37.5°C, intermittent or constant) for more than 1 month
- Persistent oral candidiasis
- Oral hairy leukoplakia
- Pulmonary TB
- Severe bacterial infections (e.g., pneumonia, meningitis, PID<sup>\*</sup>, bone/joint infection, bacteremia)
- Multidermatomal, recurrent mono-dermatomal or ophthalmic VZV<sup>\*</sup>
- Necrotizing ulcerative gingivitis, periodontitis or stomatitis
- Unexplained anemia (<8.0 gr/dl), neutropenia (<500/μl) and/or thrombocytopenia (<50,000/μl)

#### Clinical stage 4: severe disease

- HIV-1 wasting syndrome
- *Pneumocystis jiroveci* (formerly *carinii*) pneumonia
- Recurrent severe bacterial pneumonia
- Chronic HSV infection (orolabial, genital or rectal for more than 1 month or visceral at any site)
- Esophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
- Extrapulmonary TB
- Kaposi's sarcoma
- *Cytomegalovirus* retinitis or infection of other organs
- CNS toxoplasmosis
- HIV-1 encephalopathy (AIDS dementia complex)
- Extrapulmonary cryptococcosis, including meningitis
- Disseminated non-TB mycobacterial infection
- Progressive multifocal leukoencephalopathy
- Chronic diarrhea due to cryptosporidiosis and/or isosporiasis
- Disseminated mycosis
- Recurrent septicemia
- Lymphoma (cerebral or non-Hodgkin's)
- Invasive cervical carcinoma
- Atypical disseminated leishmaniasis

■ Symptomatic HIV-associated nephropathy and cardiomyopathy

HSV: Herpes simplex virus; PID: Pelvic inflammatory disease; VZV: Varicella zoster virus.

\* Not part of international WHO staging, but added as frequent Botswana-specific HIV-related 'advanced' conditions meriting combination antiretroviral therapy initiation.

Recently released data from the ongoing CIPRA HT 001 trial Data Safety and Monitoring Board (DSMB) [204] has shown that in Haiti, starting cART in adults ( $n = 816$ ) when their CD4<sup>+</sup> cell counts are between 200 and 350 cells/mm<sup>3</sup> improves survival when compared with deferring cART until their CD4<sup>+</sup> cell count drops below 200 cells/mm<sup>3</sup>. In addition, interim analysis showed that among patients initiating cART without TB at baseline, 18 persons in the early treatment (CD4<sup>+</sup> cell count of 200–350 cells/mm<sup>3</sup>) group developed incident TB compared with 36 persons in the standard-of-care (CD4<sup>+</sup> cell count <200 cells/mm<sup>3</sup>) group, a statistically significant difference [204]. Certainly, longer term follow-up and additional study data are needed, but such data do have the potential to change the standard-of-care recommendations for 'when to start' cART in resource-limited settings.

### What to start

Current US Department of Health and Human Services (DHHS) guidelines [201] recommend that qualifying HIV-1-infected adults be initiated on two NRTIs plus one NNRTI or two NRTIs plus one boosted PI. The preferred agents are coformulated TDF/FTC, EFV, and ritonavir-boosted atazanavir, lopinavir, darunavir or fosamprenavir. Alternatives include the dual NRTI combination of ABC plus 3TC, the NNRTI NVP (only in women with a baseline CD4<sup>+</sup> cell count of less than 250 cells/mm<sup>3</sup> or men with a CD4<sup>+</sup> cell count less than 400 cells/mm<sup>3</sup> due to the heightened risk for hepatotoxicity), and the unboosted PIs of atazanavir or fosamprenavir [201].

The preferred first- and second-line cART regimens for sub-Saharan Africa are a subject of considerable debate. Policymakers need to consider a range of issues when formulating national guidelines, including cost, efficacy, tolerability, the potential for drug resistance and drug–drug interactions, as well as short-term and longer term ARV treatment adherence. Several national initiatives offering public NNRTI-based cART have recently commenced in sub-Saharan Africa. Preliminary outcomes data from ARV pilot studies in Côte d'Ivoire [19], Senegal [20], Uganda [21], Khayelitsha, South Africa [22] and Botswana [23], as well as preliminary data from larger public cART initiatives in Malawi [24,25], Botswana [26] and Zambia [27], have documented favorable outcomes among the vast majority of cART-treated adults.

### Nucleoside reverse transcriptase inhibitors

The WHO guidelines issued in 2003 recommended a five ARV formulary approach for first-line use: 3TC plus ZDV or d4T plus NVP or EFV [203]. In 2006, this recommendation was revised to include TDF or ABC as alternative first-line NRTIs while advising policymakers to 'move away' from d4T-containing regimens in an attempt to minimize or avoid the potential mitochondrial toxicities associated with this ARV medication. In sub-Saharan Africa, the majority of cART-treated adults are presently receiving d4T (or ZDV) and 3TC plus either NVP or EFV. Women with reproductive potential are initiated on NVP-based cART owing to the potential teratogenicity of EFV.

Most recently, many countries in the region, including Botswana, Zambia and, on a smaller scale, Nigeria, have switched to TDF-based cART, administered with FTC as the



coformulation Truvada™. This regimen is in line with resource-rich recommendations and avoids the potential toxicities associated with ZDV and d4T use. There are, however, a few smaller case series that have reported poorer virologic outcomes among adults receiving first-line TDF, FTC and NVP [28], which warrants consideration and close monitoring of the initial group of adults treated with this regimen in sub-Saharan Africa.

In the analysis of data from the ART-LINC collaboration [29], which included adults receiving cART at 17 programs in 12 countries in sub-Saharan Africa, South America and Asia (n = 36,715), median CD4<sup>+</sup> cell count at the time of cART initiation (baseline) increased in Africa in recent years (2005–2006) to 122 cells/mm<sup>3</sup> [IQR: 53–194] where the majority of cART-treated patients (56%) received d4T/3TC and NVP. In all regions, females had higher median CD4<sup>+</sup> cell counts than men at the time of cART initiation, with an average of 22 cells/mm<sup>3</sup> higher in Africa [29].

### ZDV/didanosine inferiority

Interim data from a large randomized clinical trial conducted in Botswana has shown that the proportion of participants with virologic failure and genotypic resistance mutations was 11% in those receiving ZDV/didanosine (ddI)-based cART versus 2% in those receiving either ZDV/3TC- or d4T/3TC-based cART (p = 0.002) [23]. The median CD4 T-cell count increase at 1 year was 137 cells/mm<sup>3</sup> (IQR: 74–223) and 199 cells/mm<sup>3</sup> (IQR: 112–322) at 2 years with a significantly lower gain in the ZDV/ddI arm [23]. At 1 and 2 years, 92.0 and 88.8%, respectively, of patients had an undetectable plasma HIV-1 RNA level (≤400 copies/ml) [23]. Additional analyses suggested a trend towards poorer adherence among ZDV/ddI-treated participants, and anecdotally study participants frequently expressed difficulty following the specific food-related instruction (i.e., the need to take it first thing in the morning on an empty stomach) when taking the nonenteric-coated ddI [23]. How these findings relate to the efficacy of ZDV/ddI as the dual NRTI back-bone for second-line cART regimens remains unknown and a necessary area of future research.

### TDF considerations

Owing to the potential of TDF for bone mineral density changes, including demineralization and bone porosity effects, TDF is currently not recommended in pregnancy. Consensus regional recommendations state that all women identified as pregnant should be immediately switched to ZDV/3TC plus NVP if they have a CD4 cell count of less than 250 or 200 cells/mm<sup>3</sup>, depending on existing national ARV guidelines. Women often continue their ZDV-based regimen post-partum if they have not experienced any ZDV-related or exacerbated side effects [202].

Tenofovir also has the potential to cause renal insufficiency or failure from renal tubular insult, and therefore creatinine clearance must be calculated and recorded at baseline, 3 and 6 months following cART initiation, and if stable, every 6 months thereafter. Reliance on serum creatinine as a surrogate marker for creatinine clearance is inappropriate, as significant glomerular filtration rate reductions can occur before serum creatinine values become abnormal [202]. Creatinine clearance can be estimated from formulas using age, gender, body mass and serum creatinine. If a person's baseline creatinine clearance is less than 60 ml/min, TDF should not be initiated. If a person's creatinine clearance reduces to less than 50 ml/min while receiving TDF, an HIV clinician should be immediately consulted so the appropriate casemanagement steps can be taken [202].



## Non-nucleoside reverse transcriptase inhibitors

Based on available data from numerous clinical trials [11,12,30-35], EFV is the NNRTI of choice in resource-rich settings and is 'preferred' for first-line cART along with two NRTIs, usually TDF and FTC [33-35,201]. This recommendation is based on impressive efficacy and more favorable tolerability data [11,12,27-35,201]. In resource-limited settings, the majority of cART-treated adults are female [22,26,27,36,37] and have been placed on NVP-based cART regimens due to the potential teratogenic effects of EFV. In addition, recent data have also shown that maternal NVP efficacy may be significantly compromised when administered to women within 6 months of receiving single-dose (sd) NVP for PMTCT purposes [38]. NVP-based cART regimens are available generically as Triomune™, a coformulated tablet containing NVP, d4T and 3TC [1,16,203].

## Compromised efficacy of NVP-based cART among women with prior/recent sd NVP exposure

Preliminary efficacy data are available from women enrolled in the Adult AIDS Clinical Trials Group (AACTG 5208/OCTANE) study [39] from eight sites in sub-Saharan Africa. In this study, 243 women with prior sd NVP exposure at least 6 months previously and 502 women without prior sd NVP exposure received TDF/FTC with either NVP or LPV/r [39]. Analysis of the data of women with prior sd NVP exposure revealed that significantly more women in the NVP arm (n = 31 [26%]) than the LPV/r arm (n = 10 [8%], p = 0.0007) reached the primary end point of virologic failure. This effect was greatest among women initiating cART within 6–12 months of sd NVP and appeared to diminish with increasing time between sd NVP receipt and cART initiation. Investigators concluded that TDF/FTC plus LPV/r is superior to TDF/FTC plus NVP in women with prior exposure to peripartum sd NVP [39].

Studies in Botswana [38] show that women recently receiving sd NVP for PMTCT had higher rates of virologic failure when subsequently treated with NVP-based cART compared with women treated with NVP-based cART without recent sd NVP exposure. However, this applied only when NVP-based cART was initiated within 6 months following sd NVP [38].

Based on these results, many countries in the region now specify that nonpregnant women qualifying for cART initiation who have had sd NVP exposure for PMTCT within the previous 6 months should be initiated on TDF/FTC (or 3TC) plus LPV/r [38-41,202]. Nonpregnant women initiating cART who received sd NVP for PMTCT greater than 6 months ago should be initiated on standard first-line cART of TDF/FTC or ZDV/3TC with either NVP or EFV, but must be closely monitored for evidence of virologic failure [202]. One additional safeguard adopted in Botswana and incorporated into the most recent national ARV treatment guidelines in November 2008 specifies that all women who have received sd NVP for PMTCT at any time in the past and are initiated on NNRTI-based cART require close monitoring for virologic failure [202].

## NVP versus EFV outcomes

The 2NN trial [42], a large adult randomized trial, compared HIV-1-infected adults (n = 1216) receiving the dual NRTI combination of d4T plus 3TC with either NVP or EFV in North and South America, Australia, Europe, South Africa and Thailand. They found no significant differences in efficacy with NVP-versus EFV-treated patients experiencing similar rates of virologic failure. At week 48, 70% of patients taking EFV, 65% of those taking twice-daily NVP and 70% of those taking once-daily NVP had achieved undetectable plasma HIV-1 RNA levels using a lower plasma HIV-1 RNA cutoff of less than 50 copies/ml [42]. Additional 2NN analyses [42], however, did demonstrate that NVP was associated with higher rates of serious (i.e., grade 3 or higher) toxicities.

At or near the time the 2NN trial was completed, Boehringer-Ingelheim Pharmaceuticals, Inc. issued a letter to healthcare professionals [43] detailing these and related findings with advice against the use of NVP-based cART to women with baseline CD4<sup>+</sup> cell counts of more than 250 cells/mm<sup>3</sup>. This warning was based on an observed increased risk (up to 12-fold) for NVP-associated hepatotoxicity. Similar recommendations were made for men, but the baseline CD4<sup>+</sup> cell count threshold was set higher at more than 400 cells/mm<sup>3</sup> [43]. A recently published study among private-sector-treated adults from nine sub-Saharan Africa countries [44] suggests EFV superiority when compared with NVP, a result that is similar to reports from resource-rich settings. In this observational cohort of approximately 2800 adult patients, multivariate analysis showed that NVP-treated patients had a greater risk of virologic failure (hazard ratio [HR]: 1.52 [95% CI: 1.24–21.86]), death (HR: 2.17 [95% CI: 1.31–33.60]) and regimen discontinuation (HR: 1.67 [95% CI: 1.32–32.11]) when compared with EFV-treated patients [39]. Recently presented data [36] from the Adult Antiretroviral Treatment and Drug Resistance ('Tshepo') study in Botswana, which random randomized 650 ARV-naive adults to NVP or EFV, documented no significant difference by assigned NNRTI in the time to virologic failure with resistance (log-rank  $p = 0.14$ ; NVP versus EFV risk ratio = 1.54 [95% CI: 0.86–2.70]). Rates of virologic failure with resistance were 9.6% for NVP-treated patients (95% CI: 6.8–13.5) versus 6.6% for EFV-treated patients (95% CI: 4.2–10.0) at 3 years [36]. NVP-treated females had a statistical trend towards higher virological failure rates compared with EFV-treated females (Holm corrected log-rank  $p = 0.072$ ; NVP vs EFV risk ratio = 2.22 [95% CI: 0.94–5.00]). There were no differences among males [36].

### Genotypic drug resistance patterns & differences

The rates and patterns for the development of genotypic drug resistance mutations appear to differ in HIV-1 nonsubtype B-infected adults who predominantly reside in resource-limited settings of the world compared with HIV-1 subtype B-infected adults that predominantly reside in resource-rich settings.

### Major NRTI mutations

Recent data among HIV subtype C-infected adults in Malawi have documented that 19% of persons who met WHO clinical or immunological criteria for failure and had plasma HIV-1 RNA levels above 400 copies/ml showed the following: 19% had the Q151M mutation, 56% had thymidine analog mutations and 24% had the K65R or K70E mutation [45].

In addition, the reverse transcriptase mutation K65R can be selected by TDF, ddI, ABC and d4T, and leads to reduced susceptibility to all clinically used NRTIs except ZDV [46-50]. Wainberg *et al.* previously described the rapid emergence of the K65R mutation by week 12 in subtype C virus in cell culture when exposed to TDF compared with other subtypes (A, B, D, CRF\_AE, CRF2\_AG, and HIV-2). The group showed that subtype C isolates had unique polymorphisms in RT codons 64, 65 and 66, which were absent in other subtypes [51].

Additional studies have highlighted the preferential emergence of K65R in subtype C-infected patients failing d4T/ddI-based cART regimens in Botswana (30%), and d4T/3TC-based regimens in South Africa and Malawi (7–20%) [51-56]. By contrast, K65R was present in only 1.8% of HIV-1 subtype B-infected patients failing d4T-based regimens in the Stanford HIV Resistance Database. It appears to be most common in patients failing TDF-based regimens, where it is found in up to 15% of these patients [52,56-59]. The underlying reason for the more rapid selection of the K65R mutation among subtype C-infected adults does not appear to be related to enzyme-based mechanisms [52] but more research is needed. Based on these studies, HIV-1 subtype C-infected adults treated with TDF-based regimens will need to be carefully monitored for the possible selection of K65R [52,53].

Interim data from a large randomized clinical trial conducted in Botswana have shown inferiority in primary end point among adults treated with ZDV/ddI-containing cART when compared with those treated with either ZDV/3TC- or d4T/3TC-containing cART [22,60]. The 67N 70R 215Y genotype with wild-type mutations at codon positions 41 and 210 was a dominant pattern of NRTI-associated mutations at the time of virologic failure [60]. Although limited by small numbers, these data on the 67N 70R 215Y genotype with wild-type amino acids at codon positions 41, 210 and 219 in HIV-1 subtype C infection suggest that the evolution of ARV-associated mutations and thymidine analog mutation pathways may be unique in non-B subtypes treated with certain cART regimens [60].

### Major NNRTI mutations

Research has shown HIV-1 subtype C variants, the prevalent circulating subtype in southern Africa, contain a valine codon 106 polymorphism (GTG) that facilitates a V106M transition (GTG $\leftarrow$ ATG) following selection with EFV [61]. Prior to this report, V106A was listed as a NVP-specific mutation while V106M was not recognized. It is now widely believed that this V106M mutation represents a signature mutation among HIV-1 subtype C-infected persons treated with EFV, which possesses the potential to confer high-level multi-NNRTI resistance [61].

The most common major NNRTI mutations identified in patients with virologic failure in the recently completed Adult Antiretroviral Treatment and Drug Resistance ('Tshepo') study in Botswana were as follows: K103N (34.8%), G190A (28.3%), V106M (17.4%), Y181C (13.0%) and V108I (4.8%) [36].

### Survival/mortality

Despite the recent successes of the rapidly expanding number of ARV treatment sites in sub-Saharan Africa, an analysis by the ART-lower income county (ART-LINC) collaboration found that the adjusted HR (AHR) of mortality among cART-treated adults in resource-limited settings was 4.3 (95% CI: 1.6–11.8) during the first months of cART compared with those treated in resource-rich settings [62]. The AHR dropped from 4.3 during the first 6 months following cART initiation to 1.5 (95% CI: 0.7–3.0) during months 7–12 [62]. Additional data from this group [63] evaluating 5491 adult patients found that the incidence of early patient loss increased when programs were scaled-up and were associated with fee-for-service and advanced immunosuppression at baseline. Overall, 3.8% of patients had no follow-up, 16.0% were lost to follow-up and 2.8% were known to have died in the first 6 months following cART initiation [63]. Another study by Bisson *et al.* in Botswana found that over half (58.8%) of patients deemed 'lost to follow-up' were confirmed dead after intensive tracing. In addition, they concluded that a significantly increased risk of death following cART initiation among men (AHR: 1.74; 95% CI: 1.05–02.87) would have been missed had these patients not been traced in their respective communities [64].

Lawn *et al.* have documented that between 8 and 26% of patients receiving cART in sub-Saharan Africa die within the first year of treatment, with the majority of these deaths occurring in the first few months of treatment [65,66]. Baseline characteristics that are independently associated with early mortality risk include low CD4<sup>+</sup> cell count, advanced WHO clinical stage disease (stage 3 or 4 disease), low BMI (<18.5), anemia and male gender [65]. In numerous programs in Africa [65,66], the median CD4<sup>+</sup> cell count values at the time of cART initiation are low, in the range of 100 and 150 cells/mm<sup>3</sup> [65-72], and this has been highlighted as a significant contributing factor to high early mortality rates [65,66]. In their most recent analysis of 2423 adult patients, Lawn *et al.* documented mortality rates for up to 5 years of follow-up at 8.1%, and a multivariate analysis showed that patients who had a baseline CD4<sup>+</sup> cell count of less than 100 cells/mm<sup>3</sup> had significantly higher cumulative mortality estimates at 1 and 4

years (11.6 and 16.7%, respectively) compared with patients whose baseline CD4<sup>+</sup> cell count was at least 100 cells/mm<sup>3</sup> (5.2 and 9.5%, respectively). Investigators contend that these discrepancies were largely due to greater cumulative person-time being spent in what is now being referred to as the ‘death zone’ (i.e., CD4<sup>+</sup> cell count values <200 cells/mm<sup>3</sup>) [65,66].

Bussmann *et al.* recently published results from a trial of 633 public cART-treated adults in Botswana [26] with Kaplan–Meier survival estimates at 1, 3 and 5 years of 82.7, 79.3 and 79.0%, respectively. Adjusted mortality rates showed similarly high early mortality rates when compared with other cohorts of adults initiating cART with severe baseline immunosuppression [31,66–74]. Mortality in this cohort was highest in the first year, with 50% dying in the first 3 months and approximately 86% of all deaths occurring within the first year. The majority of deaths were secondary to advanced AIDS, with only a small fraction attributed to ARV-related toxicities. In addition to the high early on-treatment mortality, another concern was the significant number of patients that qualified to receive cART but died prior to cART initiation, further emphasizing that a swift and decentralized roll-out of ART programs in high-prevalence countries is urgently needed [75,76].

### Tolerability/toxicity Rates of ARV-related toxicities in sub-Saharan Africa

A recent meta-analysis review of 28 articles and abstracts from 14 African countries [77] found that an overall median of 21.2% of patients had experienced drug toxicity, although there were few cases of grade 3 or 4 events. A Swiss cohort study [78] found that 47% of patients presented with clinical adverse events while on treatment with ‘PI-sparing’ cART regimens, which most of the African studies employed. The most commonly reported toxicities were emesis, mood disorders, elevated amylase levels, elevated glucose levels, lactic acidosis, neutropenia and elevated alkaline phosphatase levels [78]. Using data from 153 patients enrolled in Botswana’s public ART pilot program [18], a Kaplan–Meier estimate of toxicity within the first year of ART was 23.8% (95% CI: 15.5–31.2%), with a Kaplan–Meier estimate of developing a treatment-modifying toxicity by year one of 32.2% (95% CI: 23.0–40.4%). In total, 47 of the 153 (30.7%) patients had treatment-modifying toxicities within the first year on treatment [18]. The study also found that 29% of these treatment-modifying toxicities were for severe peripheral neuropathy, 6% for hepatotoxicity, and 4% for ddI-related pancreatitis and NVP-related cutaneous hypersensitivity.

Additional preliminary regional data from Botswana evaluating 306 ART-naïve adults treated with PI-sparing public ZDV-based cART showed that 8.0% developed severe (grade 3–4) anemia (mean time to development = 11.6 weeks), 2.7% developed Stevens-Johnson syndrome (mean time to development = 28.0 days on ART) and 3.4% developed grade 3–4 liver function test abnormalities (mean time to development = 12.6 weeks) [79]. This initial group of cART-treated patients was significantly immunocompromised at the time of ART initiation, with a median CD4<sup>+</sup> cell count of 81 cells/mm<sup>3</sup> and a median plasma HIV-1 RNA level of 442,000 copies/ml, with 89.2% of patients having WHO clinical stage 3 or 4 disease.

Data of longer term ART outcomes from Khayelitsha, South Africa [80] have shown similar toxicity rates from 287 adults with advanced baseline HIV-1 disease (median CD4<sup>+</sup> cell count of 43 cells/mm<sup>3</sup> and mean plasma HIV RNA level of 151,000 copies/ml) treated with ZDV/3TC-based cART with either EFV (60%) or NVP (38%). In this cohort, the cumulative probability of changing a single ARV medication by 24 months was 15.1% due to toxicity or contraindications, and 8.4% due to toxicity alone. Most changes occurred soon after cART initiation (median time: 42 days; IQR: 28–56 days). Additional data from this cohort showed that after 24 months of therapy a similar proportion of patients had switched from d4T, ZDV and NVP due to toxicity (8.5, 8.7 and 8.9%, respectively) [81]. By contrast, only 1.7% had switched from 3TC. Most drug regimen changes (36 of 44, or approximately 82%) were attributable to anemia among ZDV-treated patients. Data from Uganda (n = 137) among adults

receiving d4T- and 3TC-based cART with primarily NVP (77%) or EFV (14%) showed that 55% of patients experienced some level of discomfort, with 51% reporting pain, numbness, tingling of the hands or feet and skin rash with dryness or pruritus. Rash was reported in 49% of the 125 patients treated with an NNRTI-containing regimen [82].

Interim data from a large cohort of ART-treated adults in Botswana receiving ZDV/ddI, ZDV/3TC or d4T/3TC with either NVP or EFV (n = 650 total) showed that 17.7% of patients experienced a treatment-modifying toxicity [83]. The most common toxicities were anemia (3%), lipodystrophy (3%), grade 3 hypersensitivity cutaneous reactions or Stevens–Johnson syndrome (3%), neutropenia (2%), lactic acidosis (1%), moderate-to-severe symptomatic hyperlactatemia (1%), hepatotoxicity (1%), neuropsychiatric symptoms (1%) and pancreatitis (1%). Completed 3-year study data from this study showed that 140 patients had 178 treatment-modifying toxicities (27.7% NVP vs 15.7% EFV; p = 0.0001). Pertinent treatment-modifying toxicities include the following: 20 (6.2%) NVP-treated patients developed cutaneous hypersensitivity reactions, seven (2.2%) EFV-treated patients developed neuropsychiatric symptoms, and 11 (3.4%) of NVP-treated and three (0.9%) EFV-treated patients developed hepatotoxicity, excluding lactic acidosis [36].

Preliminary data from southern Africa [77,80-84] have shown differences in the patterns and rates of toxicities among HIV-1 subtype C-infected adults when compared with HIV-1 subtype B-infected, ART-treated counterparts in resource-rich settings. Keiser *et al.* compared cART-treated adults in Cape Town, South Africa (n = 2348) to those treated in a Swiss Cohort (n = 1016) [85]. Treatment changes due to toxicity in the first 3 months following cART initiation were more frequent in Switzerland than in South Africa, despite the fact that Switzerland had greater first-line medication options, with more favorable toxicity profiles. The type of treatment-modifying toxicities were fairly similar in the two settings, with the exception of symptomatic hyperlactatemia or lactic acidosis, which was documented in 32 South African patients, but not observed in Switzerland [85]. Preliminary regional data reveal a higher than expected rate of lactic acidosis (1.0–1.1%) among ART-treated adults, and its development appears to be related to female gender, body habitus (being overweight, BMI >25 or body weight >75 kg), and use of one or more ‘D’ drugs (d4T or ddI). Reasons for the higher rate of lactic acidosis remain to be fully elucidated but most likely involve host genetic factors. More in-depth studies are underway. Early on (2002–2004) in public-ART-treated cohorts, there were significant rates of ZDV-associated anemia, as high as 8%. Anemia can pose a significant problem, especially in more remote areas where patients travel long distances to reach a district or referral hospital and where blood supplies are low. Preliminary data have also shown that ART-treated adults in Africa appear to have higher than expected rates (as high as 2.7%) of NVP-associated cutaneous hypersensitivity reactions including Stevens-Johnson syndrome and lipodystrophy when compared with subtype B-infected patients [77,79,86].

Rates of lipid abnormalities, defined as cholesterol and triglyceride elevations, are not yet known, as few patients have received PI-based ART for prolonged periods of time in sub-Saharan Africa. Patients may develop degrees of lipid profile changes secondary to d4T or EFV exposure, and cART-treated adults, the majority of whom are female in sub-Saharan Africa, have experienced significant rates of body habitus changes – namely lipoatrophy involving the buttocks, thighs and face – especially those who have been on cART for more than 2 years. These body habitus changes have been attributed to d4T use and, along with the higher than expected rates of lactic acidosis, are prompting many policymakers to reconsider first-line cART options for their public ART programs. In the near future, public cART programs will move away from ZDV-or d4T-based cART regimens and switch to TDF-based first-line ART regimens, which have more favorable tolerability profiles.



### Opportunistic infections Hepatitis B co-infection

Emtricitabine, 3TC and TDF all have significant activity against both HIV-1 and HBV infection [201]. Discontinuation of any of these ARV medications, however, may cause serious hepatocellular damage resulting from reactivation of HBV [87-89,201]. One study evaluating consecutively screened adults prior to cART initiation in Botswana [90] documented that 15 (10.6%) of 141 patients tested positive for hepatitis B surface antigen, with hepatitis B e antigen detected in six (40%) of the 15 hepatitis B surface antigen-positive adults. Of 140 evaluated patients, 82 (58.2%) tested positive for core IgG antibody, and 52 (37.1%) had positive results for surface antibody.

Of note, in this Botswana study, HCV antibodies were not detected in any of the 50 patients screened [90]. However, another larger (n = 1,779) study conducted in HIV-1-infected individuals in Nigeria identified 11.9% of patients as positive for hepatitis B surface antigen and 4.8% tested positive for HCV antibodies [91]. These data suggest that periodic HCV surveillance should be undertaken, especially in 'higher-risk' areas where HCV transmission may be more likely to occur, including prevalent intravenous drug use settings, settings where scarification/other 'at-risk' practices are widespread and among blood transfusion recipients where blood banks have very limited or unreliable HCV screening capacity.

### *Mycobacterium tuberculosis* co-infection Timing of cART initiation

In HIV-1-infected adults with TB who have CD4<sup>+</sup> cell count values below 200 cells/mm<sup>3</sup>, cART improves survival [92] but can be complicated by toxicity, especially hepatic and cutaneous toxicity, and the development of immune reconstitution inflammatory syndrome (IRIS). One study analyzing hypothetical cohorts, each having 1000 patients, evaluated 1-year mortality rates as well as the development of incident AIDS-defining conditions, severe IRIS and/or severe ARV medication-related toxicity in three groups of patients:

- 'Early integrated' treatment: cART initiated as soon as possible after commencing TB treatment (within 2 months);
- 'Later integrated' treatment: cART initiated once the intensive (2-month) phase of TB treatment has been completed, typically in months 3–4 of TB treatment;
- 'Sequential treatment': for this group, cART was only initiated once the TB treatment had been completed, typically 6–8 months after starting TB treatment [92].

When evaluating rates of mortality, the primary outcome, early cART was favored, even with the highest rates of IRIS (70%) and severe ARV medication-related toxicity (56%). In this model, deferred cART was favored over early cART only if the IRIS-related mortality rate in the early cART-treated group exceeded 4.6%. These results favor the early initiation of cART in HIV-1 and TB co-infected adults with advanced immunosuppression (CD4<sup>+</sup> <200 cells/mm<sup>3</sup>), except when IRIS-related mortality exceeds 4.6%. Preliminary regional data suggest that although TB IRIS mortality rates are not insignificant, they do not presently appear to exceed 4.6%. A research group in Brazil commented on the lack of definitive data answering this important question [93]. Brazilian national standard-of-care is currently to initiate cART 4 weeks after TB treatment has been started and to include rifampicin in the first-line TB regimen. In results from a study that treated patients with culture-proven TB between January 2000 to August 2006 with anti-TB therapy (ATT), this group reported 19.8% TB-related deaths, with 50% of these deaths occurring within the first 3 months following TB diagnosis. They also reported lower rates of paradoxical reactions (6.6%) than what has been reported elsewhere. They observed no increased incidence of TB IRIS and did not record any TB IRIS-related deaths [93].

Another study, the Starting Antiretroviral Therapy at Three Points in Tuberculosis Therapy (SAPIT) study, is a randomized open-label trial that recruited 645 adults diagnosed with acid fast bacilli smear-positive TB in South Africa [205]. Study participants were randomized to commence once-daily cART consisting of ddi/3TC and EFV at one of three specific times during their course of TB treatment. The three time frames were early integrated, later integrated and sequential treatment, as described previously.

The study's DSMB decided to terminate the sequential treatment arm after an interim analysis showed that patients in the other two arms (early integrated and later integrated) had a 55% lower death rate when compared with sequential treatment arm-treated patients ( $p = 0.005$ ). There were no significant baseline characteristic differences between study groups. Based on these interim DSMB findings, all patients initially randomized to the sequential treatment arm were offered cART. Patients in the two integrated treatment arms continued in active follow-up to determine whether there was any significant outcome difference between these 'integrated treatment' strategies [205].

Based on this and other data, patients who are receiving cART, and who develop active TB, can continue cART while ATT is initiated, with close monitoring for any potential toxicity, especially hepatotoxicity and rash [202]. For HIV-infected adults who have active TB and who have not yet been initiated on cART, it is often prudent to just treat the TB first [202] if their CD4<sup>+</sup> cell count is greater than 250 cells/mm<sup>3</sup> and they have not experienced a WHO clinical stage 3 or 4 event. Several other ongoing studies will address this critically important question of optimal timing of cART initiation in HIV-1 and TB co-infected adults requiring treatment for both diseases (i.e., Adult Clinical Trials Group A5221 and the ANRS sponsored Cambodian CAMELIA study), but until such results become available it is prudent to continue to individualize such decisions, taking into consideration both immunologic and clinical status.

The clinical management strategies described later are from the latest version of the Botswana national ARV treatment guidelines [202], stating that patients should be treated on a case-by-case basis, taking into consideration both immunologic and clinical status. All TB patients who have a CD4<sup>+</sup> cell count of over 250 cells/mm<sup>3</sup>, but who have another active WHO stage 3 or 4 condition, should be initiated on cART at 2 months following ATT initiation. If the WHO stage 3 or 4 condition is life-threatening, cART should be initiated much sooner following ATT initiation, with the exact timing of cART initiation depending upon the seriousness of the underlying medical condition. All multidrug-resistant TB patients who have a CD4<sup>+</sup> cell count value of more than 250 cells/mm<sup>3</sup> can be initiated on cART at 2 months after ATT initiation, with close monitoring for additive medication toxicities, especially hepatotoxicity [202]. If the CD4<sup>+</sup> cell count is below 100 cells/mm<sup>3</sup>, cART may be started as early as 2 weeks following the initiation of ATT, especially if the patient's clinical condition is poor. If the CD4<sup>+</sup> cell count is between 100 and 250 cells/mm<sup>3</sup>, cART can be started within 2 months following ATT initiation, after the intensification phase. If the patient's clinical condition is poor, cART can be initiated earlier at 2–4 weeks after TB treatment has commenced, although treatment should be handled on a case-by-case basis. Adults who have other serious AIDS-defining or HIV-related events may be initiated on cART as early as 2 weeks following ATT initiation, but must be monitored for hepatotoxicity and TB exacerbation, especially during the first 6 months after cART initiation when IRIS is most likely to occur. All adults with active TB should be initiated on cotrimoxazole for *Pneumocystis carinii* pneumonia prophylaxis, one double strength tablet (160/800 mg) administered once daily.

One large, observational study from South Africa evaluated virologic responses at 6 months in patients treated with an NNRTI-based regimen with or without TB treatment that contained rifampicin. Among the NVP-treated patients, the rate of virologic failure was higher among those with TB compared with those without TB (16.3 vs 8.3%; adjusted OR: 2.1; 95% CI: 1.2–



3.4). No difference in virologic response was seen when comparing TB versus non-TB patients who were started on EFV-based regimens [94]. NVP drug–drug interactions with rifampicin coupled with the heightened risk for hepatotoxicity among co-infected and treated adults also restricts the use of NVP among adults with active TB, although recently published data demonstrate noninferior outcomes among large numbers of HIV-1 and TB co-infected adults receiving NNRTI-based cART in Botswana [95].

### Immune reconstitution inflammatory syndrome

Some patients while on treatment for active TB will develop IRIS, which is characterized by findings such as fever, new or worsening lymphadenopathy, worsening of pulmonary infiltrates and pleural effusion. Owing to the lack of standardized IRIS case definitions, the International Network for Study of HIV-Associated IRIS team recently published case definitions that can be utilized by healthcare providers in resource-rich as well as resource-limited settings [96]. IRIS reactions may occur in the absence of HIV-1 infection and without cART, but are more common after the initiation of cART in patients with active TB disease as a consequence of immune reconstitution. One review stated that IRIS had been reported in 8–43% of patients with HIV/TB co-infection and may contribute to the higher mortality from ART in the first year of treatment [97]. Risk factors for the development of IRIS include advanced immunosuppression ( $CD4^+$  cell count of  $<50$  cells/ $mm^3$ ), severe TB disease with high pathogen burden, and interval between initiation of TB and HIV treatment of less than 30 days [97-102,201]. Most IRIS in HIV-1 and TB co-infected individuals occurs within 3 months of the initiation of TB treatment. Delaying the start of cART for 2–8 weeks may reduce the incidence and severity of IRIS but must be balanced against the potential benefit of earlier cART initiation in improving immune function and preventing HIV-1 disease progression.

Interim findings from the Tshepo study team in Botswana documented 106 incident opportunistic infections (OIs) among 93 study participants [23,83]. A total of 44 patients had a total of 50 incident OIs within the first 6 months following cART initiation; these are believed to be linked to IRIS. When stratified by baseline  $CD4^+$  cell count of under 51, 51–200 or 201–350 cell/ $mm^3$ , a marginally significant difference was found in the number of patients with an OI within 6 months ( $p=0.05$ ) of cART initiation, with those in the lowest baseline  $CD4^+$  cell count group experiencing more OIs than the other two  $CD4^+$  cell count groups [23,83]. The most frequent IRIS reactions were pulmonary TB (39%) and cutaneous zoster (37%). High rates (15–45%) of IRIS among cART-treated adults with pre-existing OIs have been reported in resource-limited settings [20,103-106]. While *Mycobacterium tuberculosis* co-infection is prevalent in this setting [103], the lower than expected frequency of IRIS could be explained by the high rate of enrolled patients (16.2%) who had received recent full courses of ATT, as well as the overwhelming majority of other patients without recent active TB who received 6 months of TB preventative therapy with isoniazid.

### Incident opportunistic infections

Incident OI rates are important markers for understanding the clinical course of treated HIV-1 disease and developing treatment guidelines and planning health services. Unfortunately, these conditions have often not been reported on in a standardized fashion. Limited diagnostic facilities, high TB rates and difficulties defining IRIS make the task more difficult in African settings [22,23,107,108].

A few regional studies have evaluated rates of incident TB among cART-treated adults. One study evaluating a 346-person cART-treated cohort in South Africa between 1996 and 2005 showed that the TB incidence density rate ranged from as high as 3.5/100 person-years during the first year of cART down to 1.01 per 100 person-years during year 5 of cART [109]. This study revealed that incidence of TB was highest in adults with the following baseline

characteristics: CD4<sup>+</sup> cell counts less than 100 cells/mm<sup>3</sup> [109] (adjusted risk ratio (ARR): 2.38; 95% CI: 1.01–5.60), WHO stage 3 or 4 clinical disease (ARR: 3.60 [95% CI: 1.32–9.80]) and age younger than 33 years (ARR: 2.86 [95% CI: 1.29–6.34]). The risk of incident TB was not independently associated with plasma HIV-1 RNA level, previous history of TB, low socioeconomic status or gender [109]. Despite similar virologic responses to cART, CD4<sup>+</sup> cell count increases were significantly less pronounced among patients developing incident TB compared with those patients who remained TB free [109]. In addition, Lawn *et al.* evaluated a community-based cohort of 1480 adults in South Africa for up to 4.5 years and identified two to three incident TB cases during 2785 person-years of follow-up (overall incidence = 7.3 cases/100 person-years) [110]. During person-time accrued with specific CD4<sup>+</sup> cell count strata, specifically 0–100, 101–200, 201–300, 301–400, 401–500 and more than 500 cells/mm<sup>3</sup>, unadjusted TB incidence rates were 16.8, 9.3, 5.5, 4.6, 4.2 and 1.5 cases/100 person-years of follow-up, respectively ( $p < 0.001$ ). They also found that patients with low base-line CD4<sup>+</sup> cell counts (0–200 cells/mm<sup>3</sup>) had a 1.7-fold higher TB incident rate during early cART treatment (with ‘early’ being defined as the first 4 months following cART initiation) than during long-term cART treatment ( $p = 0.026$ ) [110]. The authors concluded that TB risk could be reduced by developing cART program policies that limited the time cART-treated adults remained most at risk, by having CD4<sup>+</sup> cell count values of less than 500 cells/mm<sup>3</sup> [110].

## Adherence

In resource-limited settings and in particular sub-Saharan Africa, preliminary ARV adherence statistics report that cART-treated persons are generally taking more than 90% of their prescribed doses [22,68,77,111,112] – rates which are certainly comparable to those reported among cART-treated adults in resource-rich settings. However, there is surely a publication bias, as adherence data are not collected routinely in reportable PEPFAR statistics. Despite rapidly escalating numbers of adults receiving cART in the region, certain social and cultural barriers remain that may negatively impact ARV adherence rates in the future.

As part of the interim findings from the Tshepo study in Botswana, Bussmann *et al.* reported excellent overall medication adherence rates in this randomized study of 650 cART-treated adults [23,83]. Medication adherence rates of greater than 90% at all measured time points in monthly clinic adherence assessments were reported in 89.8% of study participants after 1 year of follow-up and in 81.2% of participants after 2 years of study follow-up [23]. Pooled treatment group analysis documented statistically significant differences in adherence rates when analyzed by gender, with males having poorer overall adherence rates ( $p = 0.006$ ) [23]. In reporting 5-year outcomes data of adults receiving national program cART in Botswana, Bussmann *et al.* have also demonstrated excellent overall ARV medication adherence rates as evidenced by high rates of virologic suppression (90% or greater), a low virologic failure rate (<10%) and superior monthly ARV medication refill rates [26]. However, the decline in medication adherence over time, especially among male participants, gives rise to concern. As the long-term sustainability of cART programs in Africa will largely depend on excellent sustained cART adherence rates, it is of paramount importance for healthcare personnel to provide ongoing ARV adherence support that continually adapts to meet the needs of those involved. Adherence counseling must also specifically address the needs of males, patients with ongoing psychosocial, financial or physical problems, and others who are most at risk for poor adherence.

The issues of stigma and discrimination are important influences on treatment access and adherence. Anecdotally, there are numerous cases of cART-treated adults who do not disclose their positive HIV-1 status to their partner for fear of stigma and discrimination. Do *et al.* evaluated 300 adult cART-treated adults in Botswana's national ARV treatment program between April and May 2005 [Do N, PHIRI K, BUSSMANN H, FOYA K, MARLINK RG, WESTER CW: Social

factors influencing antiretroviral medication adherence rates among haart-treated adults in Botswana (2009), manuscript in preparation]. Using a comprehensive 87-item survey, they documented an overall 81.3% ART adherence rate, which was based on 4 day and 1 month patient recall and on clinic attendance for ART medication refills during the previous 3 months. Adults receiving cART for 1–6 months were the least adherent (77% overall) followed by those who had been receiving cART for greater than 12 months (79%). Alcohol use and abuse, the presence of depression and not disclosing positive HIV-1 status to one's partner were all predictive of poor adherence rates ( $p < 0.02$ ) [Do N, Phiri K, Bussmann H, Foya K, Marlink RG, Wester CW: Social factors influencing antiretroviral medication adherence rates among haart-treated adults in Botswana (2009), manuscript in preparation]. In addition, a regional study from Lesotho, Swaziland, Malawi, South Africa and Tanzania [113] evaluated 1457 HIV-infected adults (698 [48%] of whom were cART treated) and found a significant relationship between perceived HIV stigma and self-report of missed ARV medications over time ( $p < 0.001$ ). Individuals who reported missing more ARV medication doses also reported higher levels of HIV-associated stigma [113].

National cART program staff in sub-Saharan Africa will need to provide ongoing counseling and education to help patients recognize and overcome HIV-associated stigma. Counselors must also continue to stress the need for life-long adherence to therapy, especially when cART-treated adults may believe they no longer need their medications in the wake of significant weight gain coupled with the ability to resume normal activities. Community, school, church/mosque and political venues must be targeted to change community norms.

## Future challenges

### Cost/sustainability of cART programs

In 2002, the cost to treat an HIV-1-infected adult with cART for 1 year was approximately US \$10,000 [114]. In Haiti, the annual cost in 2002 was \$700 per patient [114]. The lowest possible price per year to treat an HIV-1-infected adult in resource-limited settings [114] in 2002 was approximately \$300, using the lowest priced generic formulations. In low- and middle-income countries, the prices of most first-line medicines decreased by 30–64% from 2004 to 2007 and by 10–40% from 2006 to 2007 [206]. These reductions in ARV medication prices have contributed significantly to the increased availability of cART [206]. The median price paid for first-line treatment (prequalified by WHO) in low-income countries in 2007 ranged from \$92 per person per year for the fixed-dose combination of d4T, 3TC plus NVP (the most widely used combination) to \$294 for the fixed-dose combination ZDV/3TC plus EFV [206]. The weighted average median price of the four combinations most widely used in first-line treatment (representing 86% of the prescribed first-line treatments in low-income countries) was \$170 per person per year in 2007 [206]. The Clinton Foundation has just recently negotiated the cost of annual generic cART down to \$90 per year in 2009.

In many sub-Saharan African countries heavily impacted by the HIV epidemic, including Kenya, Malawi, Nigeria and Zambia, the annual per capita spending on healthcare of any kind is less than \$100 [1]. Even with reduced drug costs, cART requires significant health expenditure in the form of maintenance or expansion of physical health infrastructure, healthcare worker training and retention, laboratory monitoring and other related costs. Fiscal constraints will remain a challenge for some countries as cART coverage rates increase over the next decade. Numerous national cART programs will continue to depend on strong financial support from PEPFAR and the Global Fund, in particular, with added support from the Bill and Melinda Gates Foundation, the Clinton Foundation and governments themselves.

## Optimizing patient retention

As national cART programs continue to burgeon in the region, data have shown that increasing numbers of patients are being lost to follow-up [115]. ART-LINC and IeDEA investigators using data on 5491 adult patients initiating cART in 15 treatment programs in Africa, Asia and South America found that 3.8% of patients had no follow-up, 16.0% were lost to follow-up and 2.6% were known to have died during the first 6 months following cART initiation [116]. The probability of no follow-up was higher in 2003–2004 than it was in 2000 (OR: 5.06 [95% CI: 0.28–20.0]) [115] as was lost to follow-up (HR: 7.62 [95% CI: 4.55–12.8]), but not recorded death (HR: 1.02 [95% CI: 0.44–2.36]). In this large study, compared with having a baseline CD4<sup>+</sup> cell count of 50 cells/mm<sup>3</sup> or greater, having a baseline CD4<sup>+</sup> cell count of less than 25 cells/mm<sup>3</sup> was associated with having a higher probability of no follow-up (OR: 2.49 [95% CI: 1.43–4.33]), loss to follow-up (HR: 1.48 [95% CI: 1.23–1.77]) and death (HR: 3.34 [95% CI: 2.10–5.30]) [115]. A study from Durban, South Africa, revealed similar findings, with 81.4% of 501 registered patients still being in care at 3 months following cART initiation, and 82 (16.4%) lost to follow-up; 28 (34.1%) of whom had died and 32 (39%) of these being unreachable by phone despite multiple attempts [117]. Lower baseline CD4<sup>+</sup> cell counts (<100 cells/mm<sup>3</sup>) and unemployment were independently associated with being lost to follow-up [117]. As public cART programs continue to expand in the region, it will be of paramount importance to continue to identify patients most at-risk of loss to follow-up and to develop novel measures with the necessary staff resources to maximize ART program retention in resource-limited countries.

## Expanded cART for the purposes of primary HIV-1 prevention (cART as prevention)

There is growing interest in using cART as a prevention strategy, with clinical trials evaluating the use of cART in HIV-1-infected persons in serodiscordant relationships and pre-exposure prophylaxis (PrEP) in ‘at risk’ young HIV-1-infected individuals. Proponents of the first strategy argue that cART may be a cost-effective approach to reduce HIV transmission by reducing plasma HIV-1 RNA levels, regardless of CD4<sup>+</sup> cell count. A South African WHO mathematical modeling study incorporating universal HIV testing and immediate cART initiation (regardless of CD4<sup>+</sup> cell count) predicted that HIV-1 incidence and mortality rates could be reduced to below 1% within 50 years [118,119]. Data from a Zambian and Rwandan observational study, in which the HIV-1-infected partner in a serodiscordant relationship was given cART, showed a reduction in HIV-1 incidence of 79% in the uninfected partner [118, 120]. Such an aggressive ‘cART as prevention’ approach may save considerable money over the next decades if it were to result in fewer cases of HIV infection and, therefore, fewer additional adults requiring lifelong cART. However, the impact on the level of population-level resistance is unknown, and it is uncertain whether lifelong therapy is practical when we currently struggle to treat people who meet current guidelines.

Prevention of HIV-1 transmission or viral shedding may be especially important as some preliminary data [ESSEX ME, UNPUBLISHED DATA] suggest that 25–30% of HIV-1 subtype C acutely infected adults may have prolonged viremia, defined as extremely high plasma HIV-1 RNA levels for as long as 9–12 months. Prolonged viremia also supports the community-based cART as prevention approach. Other ongoing and planned trials evaluating similar concepts include the HPTN 052 (ACTG 5245) discordant couples study in which half of enrolled participants in serodiscordant relationships will receive cART earlier in the course of their HIV-1 infection, when CD4<sup>+</sup> cell count values are in the 350–550 cells/mm<sup>3</sup> range.

Botswana is beginning to offer universal cART in pregnancy as a means to drastically curtail and hopefully eradicate mother-to-child transmission (MTCT) of HIV [202]. Other promising preliminary data regarding strategies to reduce MTCT rates were recently presented at the 16th Conference on Retroviruses and Opportunistic Infections [121]. Two of these approaches were

maternal cART during breastfeeding and extended infant ARV prophylaxis. The results of ongoing clinical trials including the KiBS (Kenya), Mma Bana (Botswana), MITRA-Plus, ZEBS (Zambia) [122], PEARL, BAN, PEPI [123] and planned large PROMISE (IMPAACT) studies will largely inform PMTCT policy in the region [121].

Another potentially promising approach using cART as prevention involves the use of PrEP, and a few ongoing placebo-controlled, randomized African PrEP trials [124] should soon yield important data. Two African trials warranting specific mention at present include: the TDF-2 trial in Botswana [125], a Phase I/II randomized double-blind placebo-controlled trial (n = 2000 individuals) of daily TDF plus FTC for healthy HIV-1-negative adults aged 18 to 39 years in Botswana and South Africa; and the Partners PrEP trial (n=3900 African discordant couples) of TDF/FTC, TDF alone or placebo for 36 months. These cART PrEP trials are especially important as data have shown that greater than 50% of new HIV-1 transmissions occur in stable couples. One potential concern with PrEP, based on data from Wainberg's group in McGill and Botswana [51], is the possibility of rapid selection and the emergence of the K65R mutation. This emphasizes the importance of monitoring for primary HIV-1 genotypic resistance in cART PrEP trials. At present, most of the research in the region has shown very little major genotypic resistance mutations to first-line cART, although continued surveillance is warranted.

### Availability of second- & third-line cART regimens

As patients receiving cART live longer in resource-limited settings, the need for second- and third-line treatment options will increase. A 2006 WHO survey of low- and middle-income countries found that 96% of patients were still reported to be on a first-line regimen [126, 127]. However, the annual rate of switching to second-line cART is forecast to increase from 5% in 2005 to 12% in 2010, representing between 500,000 and 800,000 individuals [128, 207].

The WHO recommends a PI-based second-line regimen for patients failing NNRTI-containing initial regimens [128]. Only ritonavir-boosted PIs were recommended in the 2006 WHO treatment guidelines, and subsequent publications gave preference to LPV/r, ATV/r or FPV/r. The selection of ritonavir-boosted indinavir or saquinavir was discouraged owing to concerns about poor tolerability and adverse events, especially in hot climates [116,129,130]. Currently, LPV/r is the only generic heat-stable fixed-dose combination PI widely available in resource-limited settings [131]. A fixed-dose, heat-stable formulation of ATV/r is expected to have an efficacy and tolerability profile similar to LPV/r, but at a lower pharmaceutical ingredient cost [132]. Voluntary licenses from the innovator company (Bristol-Myers Squibb) have been granted for generic production of ATV, and the WHO has declared the wide availability of a coformulated heat-stable ATV/r to be a priority [128,207].

Most first-line cART in sub-Saharan Africa incorporates 3TC and AZT or d4T, and the WHO recommends the combination of TDF plus 3TC or ABC plus ddI as second-line NRTIs for patients failing thymidine analog-containing regimens [128]. However, recent reports from Botswana, South Africa and Malawi suggest that these second-line regimens may be less effective than anticipated owing to the presence of K70E or K65R mutations at clinical or immunological treatment failure [52-55]. TDF has been selected as a first-line agent by some national HIV-treatment programs despite higher costs [133], supported in part by evidence for lower adverse event rates (especially anemia) and a more favorable resistance profile at treatment failure. For patients failing a TDF-containing first-line treatment, the WHO recommends a second-line NRTI combination of AZT plus 3TC.

Newer ARV agents may have a future role in resource-limited settings, but high cost, lack of generic alternatives, the need for expensive pre-treatment testing and poor heat stability



prohibit their extensive use at present. Etravirine is a new, PI-sparing, NNRTI option for patients failing NVP or EFV and shows increased *in vitro* potency (ten- to 500-fold) in comparison to EFV in the presence of combination mutations, including K103N with Y181C or L100I [134,135]. Darunavir and tipranavir are second-generation PIs with activity against HIV strains with multiple PI resistance mutations, and could be important treatment options for patients failing current LPV/r-based second-line regimens [125,136,137]. Raltegravir is the first member of the integrase inhibitor ARV class and initial studies have demonstrated efficacy in heavily treatment-experienced patients with multiclass ARV resistance [138]. The appropriate use of raltegravir is still being defined in resource-rich countries, but it may be a potent third-line or beyond treatment option. Maraviroc is a CCR5 chemokine receptor inhibitor that prevents viral entry and has shown efficacy in heavily treatment-experienced patients [139]. Its use in resource-limited settings is constrained by the need for a complex and relatively high-cost HIV-1 tropism assay to identify patients with susceptible virus. Enfuvirtide (T-20) is a biometric peptide that prevents fusion of the viral and host cell membranes [140]. It is primarily reserved for salvage therapy in resource-rich settings, and its use in resource-limited settings is constrained by high cost, poor heat stability and subcutaneous administration. All of these newer ARV agents were patented and approved for use by the US FDA since 2003, and generic versions are not expected to reach the market in the near future.

### Treatment monitoring & criteria for switching to second-line cART

The measurement of HIV-1 RNA levels (i.e., viral load [VL]) is recommended to determine the response to cART in developed countries [10,16], but the high cost and sophisticated laboratory equipment necessary to perform VL testing currently prohibits the use of this technology in many resource-limited areas. When VL testing is available, current WHO guidelines recommend a switch to second-line cART if the VL rises above 10,000 copies/ml. This threshold is based on limited evidence of minimal CD4<sup>+</sup> cell count decline and disease progression in patients with detectable viremia below this level [141,142]. Delaying cART switching in areas with limited second- or third-line options may preserve viable treatment regimens and improve long-term outcomes, but further data on the accumulation of resistance mutations are needed.

In areas without access to VL testing, the WHO has proposed the use of clinical and CD4<sup>+</sup> cell count-based criteria to guide treatment decisions [207], but the performance of these criteria has been poor. An assessment of 1133 patients in rural Uganda found a composite sensitivity of 23–28% and a specificity of 90% for detecting virologic failure (depending on the VL threshold) [143]. A study in South Africa among 324 patients reported a sensitivity of 21% and a specificity of 96% in detecting a VL greater than 10,000 copies/ml [144], while a study in Nigeria of 395 ‘high-risk’ patients (treatment exposed, poorly adherent or with evidence of immunologic or clinical deterioration) reported a sensitivity of 39–59% and a specificity of 59–80% (depending on the criterion) to detect a VL greater than 400 copies/ml [145]. Similar reports from British Columbia [146], South Africa [147], Thailand [148] and Uganda [149] highlight the need for improved treatment failure algorithms in the absence of VL monitoring.

Arguments to minimize VL monitoring [150] must be weighed against the health effects and unnecessary costs associated with unreliable and inaccurate diagnostic tools [151]. A computer simulation model of routine VL monitoring compared with clinical or CD4<sup>+</sup> cell count-based monitoring found a moderate survival benefit, but at an increased cost of approximately \$3500.00 per life-year gained [152]. Cost-effectiveness analyses have reported high incremental cost-effectiveness ratios for VL monitoring compared with CD4<sup>+</sup> cell count monitoring in resource-limited settings [153,154], but potential long-term savings [155].

The benefit of routine VL monitoring in resource-limited settings is uncertain because of the high costs associated with the test and the limited cART regimens. A trial in Zambia

(NCT00929604) will assess mortality at 36 months among approximately 2100 cART-naive patients initiating therapy and receiving care at facilities with access to routine HIV VL testing (at cART initiation, at 3 months and at every 6 months thereafter) compared with those initiating first regimens and receiving care at facilities with ‘discretionary’ VL testing (i.e., owing to clinical failure or immunologic failure as defined by local criteria). In Uganda, a trial (NCT00434070) of combined VL and CD4<sup>+</sup> cell count treatment monitoring versus CD4<sup>+</sup> cell count alone is recruiting participants and will assess the development of resistance mutations at 36 months associated with each strategy. These targeted evaluations will provide critical information on the potential survival benefits and effect on the development of drug resistance in resource-limited settings, in addition to urgently needed information on feasibility, acceptability and cost–effectiveness.

### Task-shifting

Sub-Saharan Africa has only 3% of the world's healthworkers and accounts for less than 1% of global health spending [1,156,157], although it has almost 12% of the world's population. To illustrate this point further, there are currently 347 physicians available for every 100,000 persons in Norway, yet there are only two physicians for every 100,000 persons in Malawi or Tanzania [1,156,157]. Numerous factors contribute to the significant manpower constraints that exist in resource-limited settings. Some of these factors include the weakness of national medical education and training programs, limited implementation of national human resource management policies, and the well-documented ‘brain drain’ of health professionals who migrate from lower paying jobs in their home countries to ‘more remunerative’ or ‘more rewarding’ work in higher-income or neighboring countries [1,158,159].

As of 2009, more than 110,000 persons are receiving public-sector-supported cART in Botswana. It is anticipated that the number of persons receiving public cART as part of the national ARV treatment (‘Masa’) program will double within the next 10 years. Similar trends and projections exist in the vast majority of sub-Saharan African countries. In Botswana and some other regional settings, longitudinal care is largely provided by physicians or medical officers who are paired in medical consultation rooms with nurses. Nurse/physician visits are scheduled approximately every 3–6 months for cART-treated persons. Presently, patients on cART also attend outpatient clinics on a monthly basis for ARV dispensing and therefore interact most consistently with pharmacy staff. Pharmacy staff provide limited screening for toxicities but primarily focus on providing adherence counseling, education and evaluation for potential drug–drug interactions. Since the majority of patient visits are clinically uneventful and there is a limited number of physicians and medical officers in the region, most patients could be fully managed by specially trained nonphysician staff such as nurses, counselors and pharmacy staff. Innovative approaches of healthcare service delivery (i.e., nurse-centered care) will need to be designed and validated in order to meet rapidly expanding patient care demands while ensuring quality care.

Recent literature and past experiences in other resource-limited settings have shown that necessary skills once possessed only by specialized physicians can be successfully transferred to nurses, general clinical workers and even community workers [157,158]. The *Medicins sans Frontieres* programs in Khayelitsha and Lusikisiki, South Africa, are largely managed by nurses [160,161]. In the Khayelitsha program, a clinical team typically consists of one physician or medical officer, two nurses and two counselors. Physicians and medical officers play a prominent role at the time of cART initiation, but routine longitudinal care visits are primarily staffed by nurses and involve physicians and medical officers only if needed. At the Lusikisiki site, nurses are in charge of the cART program and physicians and medical officers rotate through the clinics on a biweekly basis [160,161]. Other nurse-centered programs, such as the Zambian National ARV program, have also reported similar anecdotal successes [162]. With



large numbers of available locally trained nurses and uniform training and education mechanisms already in place, the majority of sub-Saharan African countries presently have the capacity to shift towards a more cost-effective and sustainable nurse-centered care approach. One possible permutation of the nurse-centered care approach would be to have four nurses trained specifically in HIV/AIDS and cART management see patients under the supervision of one on-site physician who could be available for immediate consultation. The more experienced physicians could also supervise and mentor junior physicians who are seeing patients at the same time, which would facilitate skills transfer over time and provide a more sustainable model of healthcare delivery.

To circumvent these manpower shortages, numerous sub-Saharan African countries have already switched in varying degrees to nonphysician care models, and the preliminary results are promising. Regional public programs adopting nurse-centered approaches to healthcare delivery in Haiti and Rwanda report very low lost to follow-up rates, high ARV treatment success rates and mortality rates that are comparable to those among cART-treated persons residing in resource-rich settings [1,163].

### Survival/mortality

Early mortality among cART-treated adults needs to be a primary focus in the region over the next few years. Rates of pulmonary and extrapulmonary TB, both IRIS related and non-IRIS related, are high, especially among those initiating cART with advanced immunosuppression and baseline CD4<sup>+</sup> cell count values of less than 100 cells/mm<sup>3</sup>. Planned public-health approaches to address this include the initiation of empiric ATT as part of a clinical trial in an attempt to alleviate the morbidity and mortality associated with resistant TB infections. Novel therapeutic interventional strategies to treat IRIS will be an area of focus. In addition, public hospitals will need to expand laboratory, diagnostic, microbiologic and surgical pathologic capacity providing evidence-based data that will inform public policy and help healthcare providers give high quality care to patients. These trials will also increase our understanding about the scope of resistant (multidrug resistant-TB/extensively drug resistant-TB) infections, antibiotic resistant respiratory and enteric infections, cotrimoxazole and screen for preventable cancers.

### Opportunistic infections

Over the next 5–10 years, expanded cART coverage and isoniazid preventative therapy to all HIV-1-infected adults will hopefully result in reduced TB incidence rates. The issues of how best to manage adults with incident TB who are receiving second-line cART needs to be an area of focus, as issues of overlapping toxicity (hepatotoxicity) and drug–drug interactions remain.

Coformulated LPV/r is widely used for second-line ART in both resource-rich and resource-poor settings. Owing to cost and supply chain constraints, rifabutin has largely been unavailable in many resource-limited settings [164]. However, reliable stocks of rifabutin have recently become available in India, and in March 2009, the WHO placed rifabutin on its list of 'essential medicines' but only for use in patients with HIV-1 on PI-containing regimens [165]. As part its recent meetings, the WHO's 17th Expert Committee on the Selection and Use of Essential Medicines plans to approve the use of rifabutin for the treatment of TB in the place of rifampicin among patients receiving concomitant PI-based cART. These recommendations state that dose-reduced rifabutin can be administered with normal doses of LPV/r, ATV/r, ritonavir-boosted darunavir and FPV/r [166]. Of note, the recommendations for rifabutin dosing, namely the 75% dose reduction, among HIV-1-infected adults receiving concomitant LPV/r are based on extrapolations from healthy HIV-1-negative adults receiving foamprenavir/ritonavir [166].

The March 2009 WHO essential medicine list recommendations for rifabutin, which allows it to be used in HIV-1-infected persons receiving PI-containing cART regimens, will increase the use of rifabutin for treatment of resistant TB in HIV-infected persons treated with LPV/r. There is an urgent need for data to directly confirm or refute the WHO recommendation. Pharmacokinetic studies will need to be performed among healthy HIV-1-negative adults receiving dose-reduced rifabutin and LPV/r. Findings from these preliminary pharmacokinetic studies conducted in healthy HIV-1-negative adults will assist with planning larger efficacy and outcomes trials for treating HIV-1/TB co-infection.

Tuberculosis treatment and cART services have not been well integrated in many sub-Saharan African countries where large numbers of HIV-1 and TB co-infected persons reside. Recent statistics from the Joint United Nations Programme on HIV/AIDS (UNAIDS) [1] report that only 42% of countries with generalized HIV-1 epidemics have implemented routine TB screening for HIV-positive patients, and only 27% provide TB preventative therapy in all districts in need. In addition, hundreds of thousands of persons who are co-infected with HIV-1 and resistant TB die unnecessarily each year owing to inadequate TB diagnostic services, failure to deliver affordable medications to those in need and increasing rates of TB drug resistance. Although the question of when best to initiate cART in relation to the timing of ATT will hopefully be answered by ongoing clinical trials in the next 1–2 years, considerable work needs to be done to integrate TB and HIV services, to more rapidly and efficiently diagnose active TB and drug-resistant infections, and to improve infection control practices.

### **Non-AIDS complications**

As persons survive longer on cART in sub-Saharan Africa, similar to trends in resource-rich settings, increasing numbers of cART-treated adults in sub-Saharan Africa will develop non-AIDS-defining events, which will include hepatic, renal, cardiovascular and non-AIDS-related malignancies. As an average of 4–10% of HIV-1-infected adults in the region are HBV co-infected and an unknown percentage are HCV co-infected, increasing numbers of adults will be at risk for the development of end-stage liver disease and hepatocellular carcinoma. Cancer and cardiovascular disease are the most common causes of death worldwide, and hospitals in the region will need to continually expand their diagnostic services to screen for and effectively manage these complications in HIV-infected patients over time. This will become especially important as the cART-treated populations age across the continent, as at present, a very low proportion of cART-treated adults are older than 50 years of age. This proportion, however, will increase significantly over the next 10–15 years. Cervical cancer screening has been shown to be feasible within an ART clinic context with more than 30,000 women screened in Zambia in just 2 years [123].

### **Adherence**

In addition to providing counseling and education that addresses the issue of stigma in longitudinally cART-treated adults, healthcare providers will also need to screen for the presence of depression and other mental illness, the use of concomitant traditional medications, the lack of disclosure of positive HIV-1 status, and alcohol and other substance use and abuse, all which have been shown to negatively impact ARV-medication adherence rates. In addition, preliminary data have shown that males may be at higher risk for poor adherence. Long-term follow-up, including studies evaluating sociobehavioral aspects of adherence, is still needed and continued adherence counseling and education is warranted. Adherence counselors will need to be diligent as persons experience significant quality-of-life gains and may become complacent, feeling that they no longer need their cART regimens.

In addition, much can be learned from the successes of the directly observed therapy (DOT) TB control programs, lessons which can be applied to cART-treated adults. This includes the

formal study of community-based DOT strategies, which have been largely utilized in Haiti and Rwanda by Partners in Health. Community-based DOT has been evaluated in Botswana and Southern Africa and preliminarily has not been shown to be beneficial in randomized trials owing to equivalent virologic failure rates between adherence strategies, but more research is needed in this area.

## Summary

Over the next 10 years, cART coverage rates will significantly improve across the region, with attendant increases in healthcare utilization for HIV- and non-HIV-related complications and the need for expanded laboratory and clinical services. Results of ongoing trials will greatly inform discussions pertaining to the use of cART for primary HIV-1 prevention. The annual rate of cART regimen switching due to treatment failure will increase, and bringing novel agents to market, in addition to the widely available LPV/r (i.e., ritonavir-boosted darunavir and ATV/r), needs to be a high priority of international health organizations. Newer means for the timely detection of cART treatment failure is an urgent priority and will largely be informed by ongoing trials evaluating the use and cost-effectiveness of routine HIV-1 plasma RNA monitoring in clinical care in resource-limited settings.

Physician-centered care models will not be sustainable in sub-Saharan Africa and escalating manpower constraints will require the evaluation and adoption of novel task-shifting approaches to care. Education and training programs as well as patient-retention strategies will need to be strengthened as national cART programs are expanded and growing numbers of individuals require lifelong monitoring and care.

### Executive summary

#### Update

- Significant progress has been made in terms of the numbers of total qualifying adults now receiving potentially life-saving combination antiretroviral therapy (cART) in sub-Saharan Africa, with Botswana, Rwanda, Senegal and Namibia achieving over 50% coverage rates.
- Despite impressive clinical, immunologic and virologic successes as well as excellent preliminary cART medication adherence rates, high early mortality rates, especially within the first 6 months following cART initiation, remain a significant problem.
- Certain adult individuals appear to be at heightened risk for specific medication-related toxicities, many of which are life-threatening.
- The rate and patterns of genotypic drug resistance mutations also appear to differ when compared with cART-treated adults residing in resource-rich settings, potentially due to a higher prevalence of HIV-1 subtype C infection.
- Opportunistic infections continue to cause significant morbidity and mortality in the region with HIV-1 and tuberculosis co-infected patients presenting unique and sometimes difficult clinical management scenarios.

#### Future challenges

- The use of cART for the purposes of primary HIV-1 prevention (i.e., prevention of viral shedding) is likely to expand in sub-Saharan Africa over the next 5–10 years.
- Reduction of the strikingly high early mortality following the initiation of cART and the management of HIV/TB co-infection will be priority areas for clinical research.

- Rates of non-AIDS complications will increase, necessitating enhanced laboratory and diagnostic capacity within the region.
- Physician-centered care models will not be sustainable in sub-Saharan Africa, and escalating manpower constraints will magnify the need to evaluate and adopt novel ‘task-shifting’ approaches such as nurse-centered care.
- The need for effective second-line and salvage treatment options will increase as the annual rate of switching to second-line cART is predicted to increase from 5% in 2005 to 12% in 2010, especially generic, heat-stable, ritonavir-boosted protease inhibitors.
- Newer antiretroviral agents such as second-generation protease inhibitors, integrase inhibitors and cell entry inhibitors need to be added to the armamentarium of regional public cART programs but implementation is problematic owing to the lack of generic alternatives and the frequent need for ancillary testing.
- There is increasing evidence that the immunological and clinical treatment monitoring criteria used in many resource-limiting settings perform poorly, increasing the risk of resistance development in patients with detectable viremia.
- The role of routine viral load testing in treatment monitoring is controversial given the high cost of equipment and training, and the limited repertoire of second-line treatment regimens in many programs; clinical trials to evaluate this strategy are in progress.
- Primary care infrastructures must be improved for HIV care to be integrated and sustained by African countries, anticipating a day when foreign assistance may diminish. This will also help tackle the many other problems that Africans face and that HIV exacerbates.

## Acknowledgments

We would like to thank Erika Färdig (Administration, Harvard School of Public Health, Boston, MA, USA) for her review of this manuscript.

Sten Vermund is a member of a Miraviroc Expanded Access Program Data Monitoring Board for Pfizer, Inc. We would like to formally acknowledge the funder of the Adult Antiretroviral Treatment and Drug Resistance (‘Tshepo’) study, namely the Bristol-Myers Squibb foundation, for their support of this important study and capacity building initiatives in Botswana. The Adult Antiretroviral Treatment and Drug Resistance (‘Tshepo’ study data presented and referenced in this article was also supported by the following research grants from the National Institute of Allergy and Infectious Diseases, K23AI073141 (PI: C William Wester) and P30AI 060354 (PI: C William Wester) and Harvard Center for AIDS Research (CFAR) grant evaluating the Risk Factors for the Development of Nevirapine-Associated Toxicity in Southern Africa. **The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Allergy and Infectious Diseases or the National Institutes of Health.**

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