Successes, challenges, and limitations of current antiretroviral therapy in low-income and middle-income countries

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As a result of the scale-up of antiretroviral treatment (ART) programmes and substantial financial support worldwide, an increasing number of HIV-infected individuals in low-income and middle-income countries (LIMCs) now have access to ART. Despite this progress, important questions remain on the best use of ART and how patients should be maintained on a successful regimen. This Review addresses some of the issues faced by those managing the epidemic in LMICs, including when to start treatment, choice of first-line ART, and when to switch regimens. Although the first priority must be continued expansion of access to ART, there should be a move towards starting ART earlier to treat individuals before they reach advanced stages of disease, to reduce early mortality, and to build support for improved monitoring of treatment failure. There is also a need for more randomised controlled studies to identify the long-term outcomes, cost-effectiveness of ART, and use of virological monitoring in LMICs.

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Introduction

Treatment for HIV in low-income and middle-income countries (LMICs) is at present driven by a public health approach, whereby the primary goal is to provide antiretroviral therapy (ART) to as broad a population as possible in settings in which individualised management of patients by specialised physicians is not feasible.[1] As a result of several initiatives, the availability of ART in LMICs has increased substantially since 2003. The launch of the "3 by 5" (3 million by 2005) initiative by WHO, the Joint UN Programme on AIDS (UNAIDS),[2] and the US President's Emergency Plan for AIDS Relief (PEPFAR), has led to scale-up programmes in many LMICs and access to free treatment at an increased number of sites.[1,3–9] As a result, WHO reported that nearly 1 million more people were receiving ART by the end of 2007 compared with 2006, and that the original "3 by 5" target had been met, albeit later than intended.[10] Furthermore, the number of AIDS-related deaths worldwide decreased from 2·9 million in 2003 and 2006 to 2·1 million in 2007.[11] These substantial initiatives, in combination with improved prevention efforts, have led to a stabilisation of the epidemic in many parts of the world.[1,10] However, as the number of individuals meeting the criteria for receiving ART continues to rise, the enormous potential loss of life associated with a failure to provide ART to all who need it remains. A modelling study in South Africa has, for example, projected that a rapid-growth versus a zero-growth strategy for scaling up ART could lead to the prevention of 1·3 million deaths between 2007 and 2012, which would save an additional 200 000 lives compared to that achieved under the current projected timeline for moderate ART scale-up in South Africa.[12]

Barriers to ART

Despite progress in the availability of ART in LMICs, WHO estimated in 2007 that only 27–34% of people in need of ART worldwide were receiving treatment.[10] Knowledge of one's HIV status is essential for effective management and treatment. Survey estimates from sub-Saharan Africa indicate that only 12–25% of people infected with HIV are aware of their status.[10] Although this represents a substantial increase from a decade ago, most people infected with HIV in LMICs remain unaware that they are infected. This and other substantial barriers to ART, including economic, social, logistic, and human resource issues, must be aggressively addressed before the goal of increased HIV care is realised.[13]

Economic issues

The direct cost of medication remains the most substantial barrier to successful treatment if ART is not provided free of charge.[4,6,14,15] However, even if patients were to receive medication at no cost, extreme poverty still affects their access to care. Costs associated with taking time off work to attend clinics,[16–18] transportation to treatment centres,[16] and laboratory testing[18–20] all affect patients' access, adherence, or both to ART.

Social and environmental issues

Social stigma and fear of isolation and discrimination are major challenges to screening, diagnosis, and treatment. Overcoming social stigma and fear of disclosure can substantially affect the success of treatment; disclosure of an individual's HIV infection status to family members or others can help protect against virological failure.[15] Location and environmental factors also substantially affect access to ART. Many people infected with HIV live in rural settings, where access to ART can be difficult.[6] Furthermore, environments in which mass migration occur (eg, due to search for employment or fleeing war or conflict) also present a major challenge.[21–25] Access to ART is particularly difficult for vulnerable populations,

	Study location and participants	Study details	Median baseline CD4 cell count (×10⁶/L)	
			Low-income countries	High-income countries
Keiser et al[5]	Swiss HIV Cohort Study (n=1016) and two HAART programmes in Cape Town townships, South Africa (n=2348)	Included patients that were ART-naive aged ≥16 years who had started treatment with ≥3 drugs since 2001, and excluded intravenous drug users	80	204
Braitstein et al[33]	18 programmes in Africa, Asia, and South America (n=4810) and 12 HIV cohort studies from Europe and North America (n=22 217)	Comparison of baseline characteristics and outcomes in first year of ART in patients infected with HIV-1 that were ART-naive	108	234
Egger et al[34]	4 treatment programmes in Malawi, Côte d'Ivoire, and South Africa (n=7109) and Europe and North America (n=21 718)	Data from patients that were ART-naive starting ART between 2000 and 2006	96*	192
Ferrand et al[35]	Patients attending an adolescent HIV treatment clinic in Harare, Zimbabwe (n=32)	Patients the were ART-naive aged 8–19 years	101†	..
Laurent et al[36]	HIV-1-infected adults in Cameroon (n=60)	Open-label multicentre study to determine the effectiveness and safety of generic fixed-dose nevirapine–stavudine–lamivudine	118‡	..
Kumarasamy et al[14]	Patients initiating ART between January, 1996, and October, 2004 in southern India (n=1443)	Study to describe reasons for modification and discontinuation of ART	108	..

*More advanced disease at presentation (90% *vs* 29%) in patients from low-income countries. †All presented with WHO stage 3 or 4 HIV infection. ‡92% of patients (n=55) had AIDS. ART=antiretroviral therapy. HAART=highly-active antiretroviral therapy.

Table 1: **CD4 cell count and advanced disease at presentation in low-income versus high-income countries**

including orphans, prisoners, and individuals with lower levels of education,[26] and, in many countries, a substantial sex bias exists against women, which might prevent proper screening and treatment.[27,28]

Human-resource issues

In LMICs, numbers of highly-trained health-care personnel at all levels are low, and the costs of training and remuneration can seriously affect the provision of care. A recent subject of debate concerns the merits of vertical (targeted) versus horizontal (general) approaches to health-care provision. Although a disease-specific, targeted approach has increased access to ART for millions of individuals worldwide,[2] increasing emphasis is now being placed on general investment in health-care systems, infrastructure, and human resources to address a broader spectrum of diseases.[29,30] Decentralisation of access to health services, with a shift towards community-based care and task-shifting away from physicians to trained nurses and lay health-care workers, has also been shown to increase access to ART and improve adherence and follow-up.[28,31]

Logistic issues

Due to insufficient numbers of laboratories, poor-quality equipment, and lack of access to and substantial costs of laboratory testing, decisions on when to begin or switch ART are largely based on clinical assessment alone, which might delay treatment and lead to higher morbidity and mortality.[1] Other major concerns include inconsistent drug supplies and breaks in the supply chain due the logistics and costs of distribution, particularly to rural areas, and cold-chain maintenance to ensure that temperature-sensitive medicines, particularly boosted protease inhibitors (BPIs), are kept under controlled conditions. The availability of heat-stable coformulations, such as the new fixed-dose tablet of lopinavir and ritonavir,[32] that do not require refrigeration is particularly attractive in LMICs.

There are numerous challenges for managing ART in LMICs, all of which deserve substantial attention and discussion. For the purposes of this Review, however, we will focus predominantly on clinical issues, including the need for timely diagnosis and initiation of first-line ART, clinically advantageous and cost-effective monitoring and treatment strategies, and decision making on when to switch therapy.

First-line regimens

When to begin ART

Despite recent research and advances in treatment, much debate remains about the best time to begin ART in LMICs. At present, the decision relies primarily on clinical assessment and, if available, on immunological (CD4 cell count) testing. Viral-load (HIV RNA concentration) testing is expensive and is generally less available than CD4 cell monitoring in LMICs. To facilitate access to ART for individuals who are most in need, or most likely to benefit from therapy, WHO guidelines recommend beginning ART before patients become unwell or present with their first HIV-related condition, and that, if available, immunological and virological monitoring should be used to guide when to start treatment of people with HIV and used for longitudinal monitoring.[1] By comparison with people in high-income countries, individuals in LMICs might

have very low baseline CD4 cell counts and more advanced disease by the time they start ART (table 1).[5,14,33–36] Studies from high-income and low-income nations have shown that initiation of ART at lower (fewer than 200 million cells per L) compared with higher (greater than 350 million cells per L) CD4 cell counts results in poorer outcomes, including less robust immunological recovery and more rapid progression to AIDS or death.[33,37–42] In the North American ACCORD (AIDS Cohort Collaboration On Research and Design) study, beginning treatment early showed a substantial survival advantage.[43,44] More recently, a randomised controlled trial (RCT) in Haiti was stopped early after interim analyses showed overwhelmingly that beginning ART at a CD4 cell count of 200 million to 350 million cells per L substantially improved survival compared with deferring treatment until counts dropped below 200 million cells per L.[45] Delaying ART is also associated with an increased risk of serious non-HIV-related conditions, including cardiovascular disease, malignancy, hepatic disease,[46] increased risk of drug-related toxicites,[39] and possible increased risk of immune reconstitution inflammatory syndrome.[47–50] Overall, a more timely start of ART should help to further reduce high HIV-related morbidity and mortality in LMICs.

Choice of first-line regimen

In most LMICs, first-line regimens for adults and adolescents consist of a non-nucleoside reverse transcriptase inhibitor (NNRTI) plus two nucleoside reverse transcriptase inhibitors (NRTIs; figure 1).[1] Such regimens are clinically efficacious and cost-effective, because of the availability and cheaper production costs of generic fixed-dose combinations, which has made them preferred first-line treatment options and has increased access to ART in LMICs. A fixed-dose combination of stavudine, lamivudine, and nevirapine is at present the most extensively used first-line regimen in LMICs.[1] Although not frequently used, a triple NRTI approach is supported by WHO as an alternative first-line option in cases in which NNRTI use is contraindicated (figure 1).[51–56] BPI-based regimens are generally reserved for second-line therapy, primarily because of their higher cost (figure 1).[1]

The roll-out of large-scale ART programmes that use fixed-dose combinations of stavudine, lamivudine, and nevirapine has proved highly successful,[3,36,57–59] and shows that it is possible to achieve efficacy rates similar to cohorts in high-income countries.[4,5] Recent data from the national ART programme in Malawi in over 100 000 patients started on standard first-line stavudine, lamivudine, and nevirapine showed that, from 2004 to 2007, 64·9% of patients were kept alive on ART: 96·4% on first-line, 2·9% on first-line substitutions, with only 0·3% switching to second-line therapy.[60] Despite this success, switching of first-line ART due to toxic effects

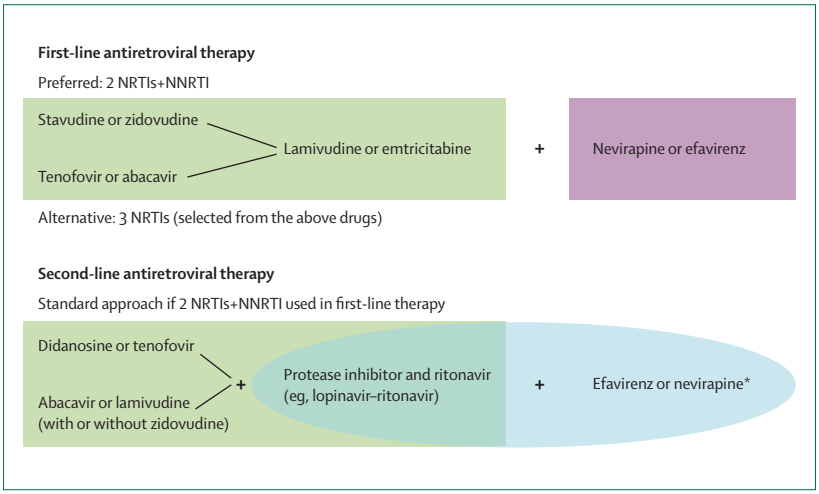

***Figure 1*: WHO 2006 recommendations for first-line and second-line antiretroviral therapy (ART)**
*Nucleoside reverse-transcriptase inhibitor (NRTI)-sparing approach if triple NRTIs used in first-line therapy. NNRTI=Non-nucleoside reverse-transcriptase inhibitor. Reproduced with permission from WHO.[1]

and drug interactions (eg, with antituberculosis medications such as rifampin) can occur, potentially limiting the durability of fixed-dose combinations.[59] Comorbidities such as tuberculosis are, therefore, yet another consideration when deciding the best time to initiate ART and the choice of first-line regimen. Loss to follow-up and early death are substantial problems in large scale-up programmes, with a wide variation in reported percentages of patients lost to follow-up (about 16–56%) and early death (about 3–48%).[61–63] Such high early mortality is probably due to a large proportion of patients having advanced disease at the start of ART. Earlier access to therapy might reduce mortality, and a better understanding of the reasons for loss to follow-up might improve outcomes.

Some African studies have shown increased peripheral neuropathy and lipoatrophy with stavudine-based regimens,[64,65] leading to concerns about the use of stavudine in first-line therapy. Issues with stavudine toxicity and increased access to newer NRTIs such as tenofovir led to a WHO guideline update in 2006,[1] expanding the NRTIs recommended for use in first-line ART in LMICs: alternatives include zidovudine or tenofovir combined with lamivudine or emtricitabine (figure 1).[1] Despite its reduced toxicity profile, tenofovir is more expensive, presenting a cost issue.[66–69] Overall, relatively few RCTs have been done to directly compare first-line regimens in LMICs, and thus limited data are available to guide the choice of first-line regimen in these settings.

Failure of first-line ART and switching to second-line regimens

Although there has been much success in terms of virological suppression with first-line regimens in LMICs,[3–5,36,57–59] a substantial proportion of patients

	WHO 2006 guidelines[1]	DHHS 2008 guidelines[79]
Virological failure	If viral-load testing is available, suggest switching at >10 000 copies per mL	Virological failure defined as viral load >400 copies per mL after 24 weeks or >50 copies per mL after 48 weeks; Virological rebound defined as detectable viral load (>50 copies per mL) after suppression.
Immunological failure	Decline in CD4 cell count to pretherapy baseline levels or below; ≥50% decrease in CD4 cell count from on-treatment peak value (if available); CD4 cell count persistently <100×10^6/L.	Failure to achieve and maintain CD4 cell counts above 350–500×10^6/L despite virological suppression; Increase in CD4 cell count of <50–100×10^6/L above baseline.

*Definition of failure for which a switch in therapy may be warranted. DHHS=US Department of Health and Human Services.

Table 2: **Virological and immunological criteria for monitoring of treatment failure***

(26–32%) still need second-line therapy.[5,15,58] The factors that influence failure of first-line ART include poor adherence to therapy, development of resistance or presence of pre-existing mutations through the transmission of resistant virus, and, particularly in LMICs, lack of a continuous drug supply.

Deciding when to switch ART regimens

The decision of when to switch therapy is particularly important in LMICs. Most patients only have access to first-line and second-line regimens, because third-line ART is not widely available in most low-income countries. Thus, if first-line ART is switched prematurely, months or years of potential effectiveness in terms of survival benefit might be lost. There might also be cost implications with the loss of cheaper first-line regimens, because second-line regimens are generally more expensive.

More commonly, if the decision to switch ART is made too late, the effectiveness of second-line therapy might be compromised because of the accumulation of resistance mutations. NRTI resistance in particular presents a major problem of drug-class cross-resistance, resulting in the loss of NRTIs that might be effective in second-line therapy. The development of multiple NNRTI mutations may currently be less of an issue in LMICs, because second-generation NNRTIs such as etravirine are not widely available.

Recent HIV-1 drug-resistance surveillance analyses in several African countries have reported transmitted resistance to be lower than 5%.[70–73] However, the scope of these surveys is limited, and the accumulation of NNRTI and NRTI resistance mutations might present future problems in terms of transmitted resistance and loss of viable first-line options. The use of single-dose nevirapine to prevent mother-to-child HIV transmission might also result in the development of NNRTI resistance, affecting the effectiveness of future NNRTI regimens.[74–76] Despite these concerns, decisions about switching to second-line ART are often dictated by regimen availability in distinct public-health systems in LMICs, rather than patient-specific issues.

Evidence from national databases suggests that a substantial proportion of patients in LMICs do not switch therapy early enough despite experiencing virological failure. In an assessment of data from 62 Médecins sans Frontières programmes,[77] of 48 338 adults followed on first-line ART, only 370 switched to a second-line regimen after a median of 20 months. Of the patients who did switch, 94% switched to a protease-inhibitor-based regimen (lopinavir and ritonavir, or nelfinavir), with good early outcomes.[77] Recent data from the TREAT Asia Observational Database showed that among 2446 patients who initiated ART, 447 developed treatment failure over 5697 person-years (7·8/100 person-years). Of these, 253 patients modified at least one drug after failure, meaning that nearly half of the cohort remained on failing ART.[31] This finding was in sharp contrast with high-income countries included in the analyses, where patients were substantially more likely to have at least two drugs modified (67% *vs* 49%) or to change to a protease-inhibitor-based second-line regimen (48% *vs* 16%).[31] A review of 3197 patients in the AIDS Healthcare Foundation Uganda Cares programme showed that 14·4% of patients had at least one regimen switch in 5 years.[78] The primary reasons for the first switch were lack of availability of current drug (27%), lipoatrophy (14·5%), avoidance of drug interactions with tuberculosis treatment (11%), and immunological treatment failure (9%). Thus, multiple factors influenced switching, with drug availability being three times more likely than treatment failure to dictate switching.[78]

Monitoring failure of first-line ART

Although virological monitoring is routine in high-income countries and is the primary method for detecting treatment failure and driving decisions to switch to second-line therapy, it is rarely available in LMICs because of costs associated with testing, lack of donor funding for monitoring, and infrastructure issues such as the availability of laboratory facilities and reagents, sufficient trained personnel, and the patient's geographic location.[1,7,9] By contrast, because CD4 cell counts are simpler and cheaper than viral-load testing, they are more commonly used. Despite this, the decision regarding when to switch therapy, as with decisions of when to initiate ART, is often based solely on patients' clinical criteria.[1]

Definition of treatment failure

Although many LMICs have their own guideline definitions of treatment failure, they are largely derived from WHO guidelines.[1] The primary guide to clinical treatment failure is the development of a new or recurrent WHO stage 4 (AIDS-defining) condition. WHO recommends, however, that other factors be taken into consideration before switching ART if treatment failure is suspected: timing (ie, after a reasonable trial of first-line therapy of 6–12 months); addressing and resolving adherence issues; waiting until the successful treatment of concurrent opportunistic infections; and excluding the possibility of immune reconstitution inflammatory syndrome.[1] However, due to lack of sensitivity, there are substantial risks associated with using clinical criteria alone to determine treatment failure.

Definitions of virological and immunological treatment failure differ widely between high-income and low-income countries (table 2).[1,79] Use of less stringent criteria, such as higher viral load and lower CD4 cell counts as thresholds for treatment failure, may lead to situations in which viraemic patients are retained on therapy, with a resultant increased risk of accumulating resistance mutations.[80–83]

Benefits and limitations of clinical, immunological, and virological monitoring

Few prospective RCTs in LMICs have been done to provide evidence on continued monitoring of patients. As a result, limited data are available to inform decisions on the optimum time to switch to second-line ART.

Incomplete virological suppression is associated with poorer gains in CD4 cell counts,[84] and large cohort studies in low-income countries have reported the use of CD4 cell counts to monitor patients in the absence of viral-load testing.[7,9] The usefulness of immunological monitoring is often dependent on having baseline as well as longitudinal CD4 cell counts available, and single or infrequent measurements might be of limited value in identifying failure or deciding when to switch. Some studies report that using immunological criteria alone could lead to misclassification of whether individuals have achieved virological suppression.[84–86] Moore and colleagues[86] found that use of the criteria of "no increase in CD4 counts" from baseline at 6 and 12 months to define treatment failure in a LMIC population led to 23–25% of patients being wrongly labelled as failing treatment, whereas their viral load indicated that they were virologically suppressed. Such circumstances could lead to patients being switched unnecessarily to second-line therapy. By contrast, a community-based HIV treatment programme in rural Africa showed that use of viral-load test results in the context of a decision-making algorithm prevented premature switching in 39 of 43 patients with suspected clinical or immunological failure.[87]

Other studies have suggested that use of viral-load or CD4 cell monitoring provides only modest benefits over clinical monitoring alone, and that, although development of cheaper assays was important, widening access to ART was the highest priority. A validated computer simulation model of first-line stavudine–lamivudine–nevirapine predicted that the proportion of potential life-years survived over 5 years would be 83% with viral-load monitoring versus 82% with CD4 cell count monitoring and 82% with clinical monitoring.[88] By contrast, another modelling study suggests that scaling up ART without access to CD4 cell monitoring could lead to an increase in the number of deaths by nearly a million by 2012 compared to programmes that include CD4 cell monitoring.[12]

There are several issues with the use of clinical criteria alone when monitoring treatment failure, not least the lack of specificity and the fact that diagnosis based on clinical (or even immunological) criteria can result in viraemic patients being maintained on ART in the presence of ongoing viral replication, with the associated risk of developing drug resistance (figure 2). In the absence of virological monitoring, there is a potentially high risk of accumulating thymidine analogue mutations (TAMs) if ART is continued in the presence of incomplete virological suppression with regimens based on zidovudine or stavudine.[83] In a recent study from Malawi, in which failure was defined using clinical criteria and CD4 cell count monitoring, extensive NNRTI or NRTI resistance was present among

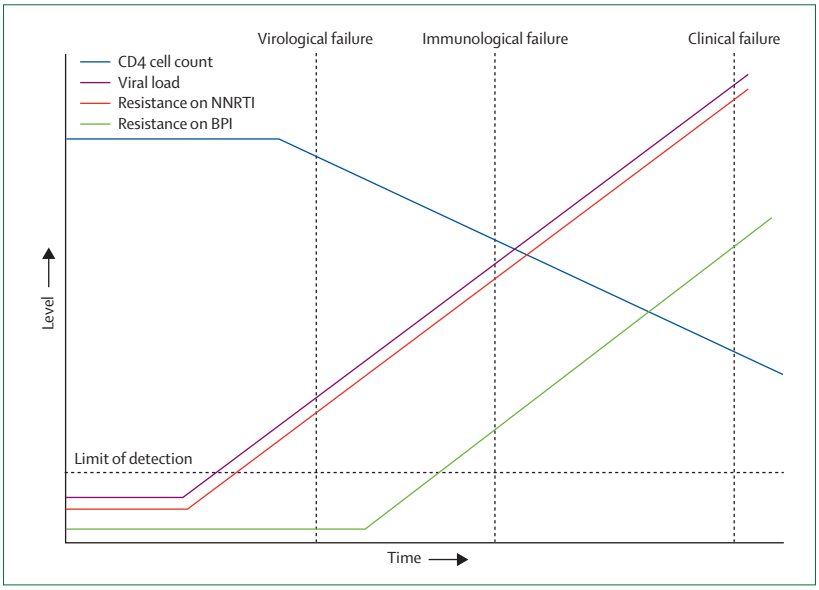

***Figure 2*: Treatment failure in the presence of ongoing viral replication**
Schematic diagram representing how individuals infected with HIV who remain on antiretroviral therapy (ART) in the presence of ongoing viral replication can have a greater risk of developing drug-resistant virus, with an associated risk of virological, immunological, and ultimate clinical failure. Mutations that cause resistance to non-nucleoside reverse-transcriptase inhibitors (NNRTIs) and protease inhibitors appear within different time frames. Resistance to NNRTI-containing regimens may be simultaneous with increases in HIV RNA concentration, but resistance to boosted protease inhibitor (BPI)-containing regimens tends to appear after detectable viraemia.

	Study location	Study type	Patients (n)	Study description	Prevalence of resistance			
					NNRTI	NRTI	TAMs	Protease inhibitor
Pillay et al[83]	Uganda and Zimbabwe	Randomised controlled trial (DART trial)	3316 (total patient cohort)	Retrospective viral load measured at baseline, week 24, and week 48 in subset of 300 patients initiating zidovudine–lamivudine–tenofovir; samples with >1000 copies per mL were sequenced. Genotypes determined for 26 (60%) of 43 at week 24 and 35 (55%) of 64 at week 48 samples with viral load >1000 copies per mL.	..	At 24/48 weeks: M184V, 65%/77%; T215F/Y 31%/51%; D67G/N 38%/60%; K70R 31%/51%; K65R 12%/14%	At 24/48 weeks: 0 TAMs 42%/26%; 1–3 TAMs 54%/37%; 4–6 TAMS 4%/37%	..
Liao et al[91]	China	National cross-sectional survey (HIVDR survey)	2689	Total incidence of resistance in patients on treatment. Patients on first-line ART: 24·6% on stavudine–didanosine–nevirapine; 20·5% on zidovudine–didanosine–nevirapine. Patients on second-line ART: 20·6% on stavudine–lamivudine–nevirapine; 11·6% zidovudine–lamivudine–nevirapine; 4·9% on stavudine–lamivudine–efavirenz; 4·0% on zidovudine–lamivudine–efavirenz.	55·1%	36·8%	..	1·7%
Sungkanuparph et al[98]	Thailand	Cohort study	98	Prevalence of resistance mutations in patients failing first-line stavudine–lamivudine–nevirapine.	92% with more than one major mutation; Y181C most common (confers resistance to nevirapine and efavirenz)	95% with one or more major mutations: M184V 89%; K65R 6%; Q151M 8%	Seen in 37% of all patients	0%
Vidya et al[99]	South India	Treatment cohort	210	Patients failing first-line nevirapine–efavirenz +zidovudine–stavudine +lamivudine (group A: 100 ART-naive patients; group B: 110 on mono or dual therapy).	..	..	66% had TAMs: 43% had TAM1 (41L, 210W, 215Y); 53% had TAM2 (67N, 70R, 215F, 219E/Q)	..
Figueroa et al[100]	Argentinean National Reference Center for AIDS	Resistance database analysis	2959 (2007 rates shown for 609)	Samples from ART-experienced patients analysed for reverse-transcriptase resistance.	103N 28·8%	Any 6·9%; 65R 2·6%; 69ins 1·0%; 151M 2·3%	6 TAMs 1·3%	..
Marconi et al[101]	KwaZulu Natal, South Africa	Cohort study	124	Patients who experienced virological failure of first-line HAART: 83·5% with more than one major mutation; 64·3% with dual-class drug resistance; 2·6% with triple-class drug resistance.	K103N 51·3%; V106M 19·1%	M184V/I 64·3%	32·2%	4·4%
Truong Giang et al[93]	Vietnam	Cohort study	248	Patients with suspected virological failure. 240 on regimens containing zidovudine–stavudine+ lamivudine+nevirapine–efavirenz: seven on triple NRTI; three on protease-inhibitor-based regimens; more than one mutation detected in 89%.	Any 88·4%; K103N 41·1%; Y181C 40·2%; G190A/S 39·2%; Y188L 12·1%	Any 95·9%; M184V 77·6%; K65R 9·4%; Q151M 7·8%; TAMs + M184V 54·3%	71·7% had more than one TAM, of which 57 (49·1%) had more than three TAMs	8·3%

ART=antiretroviral therapy. BPI=boosted protease inhibitor. HAART=highly-active antiretroviral therapy. NRTI=nucleoside reverse transcriptase inhibitor. NNRTI=non-nucleoside reverse transcriptase inhibitor. TAMs=thymidine analogue mutations.

Table 3: **Patterns of resistance**

	Study location	Study type	Patients (n)	Study description	Overall resistance profile
Gupta et al[102]	Various countries	Meta-analysis of HAART clinical trials	4212 (NNRTI-based); 3063 (BPI-based); 2684 (four cohorts from low-income countries)	Online search of PubMed and conference abstracts to compare resistance after virological failure of first-line NNRTI *vs* BPI regimens	NNRTI studies: K65R 0·13%; M184V/I 1·6%; third drug (NNRTI or protease inhibitor) 2·35%; any TAMs 0·03% Protease-inhibitor studies: K65R 0%; M184V/I 0·8%; third drug (NNRTI or protease inhibitor) 0·1%; any TAMs 0·03% Low-income countries: K65R 0·4%; M184V/I 5·55%; third drug (NNRTI or protease inhibitor) 5·93%; any TAMs 1·86%.
Ramadhani et al[15]	Tanzania	Cohort study (ADAR study)	150	Virological failure (>400 copies per mL or >1000 copies per mL) happened in 48 patients. 35 (73%) of these patients had isolates sequenced; of these 27 (77%) had successful HIV genotyping	Two (13%) had one mutation (0 NRTI, 1 K103N, 1 Y181C); seven (47%) had two mutations (7 M184V, 3 K103N, 1 Y181C, 3 G190A); six (40%) had more than three mutations (1 Q151M, 4 M184V, 1 M184I; TAMs: 1 M41L, 1 K65R, 1 L210W, 1 T215Y; 3 K103N, 1 V108I, 4 Y181C, 2 G190A)
Hosseinipour et al[89]	Malawi	National survey	101	Patients meeting definition of ART failure (Malawi national guidelines) with HIV RNA >1000 copies per mL were genotyped	55% had M184V + NNRTI mutations with more than one TAM (most common 215F/Y); 6·9% had M184V+NNRTI mutations only: 19% acquired NNRTI mutations (with or without 184V)+K70E or K65R. 16% had pan-nucleoside resistance (K65R or K70E) and additional multi-nucleoside mutations (151 complex or rare 69 insertions)

ART=antiretroviral therapy. BPI=boosted protease inhibitor. HAART=highly-active antiretroviral therapy. NRTI=nucleoside reverse transcriptase inhibitor. NNRTI=non-nucleoside reverse transcriptase inhibitor. TAMs=thymidine analogue mutations.

Table 4: **Overall patterns of resistance**

101 patients where first-line stavudine, lamivudine, and nevirapine failed (16% had pan-NRTI resistance and a further 55% were likely to have reduced susceptibility to multiple NRTIs).[89] Use of clinical criteria to define treatment failure can also lead to a situation in which individuals have faster clinical progression and advanced disease.[83,90] Switching therapy under these conditions could mean that the potential benefits of limited second-line treatment options might be compromised, with a particular risk to the preservation of future NRTI options.

The importance of adherence support in monitoring of ART

Many studies have underscored poor adherence as a major risk factor for the development of drug resistance.[91–93] Despite concerns about incomplete adherence among patients in LMICs, better adherence is often achieved compared with cohorts from high-income countries: for example, a meta-analysis of 31 studies from North America versus 27 studies from sub-Saharan Africa showed overall adherence of 55% versus 77%.[94] However, programmes to improve monitoring and further optimise adherence should be adopted to reduce resistance and the consequent need for regimen changes. A recent study from the novel home-based AIDS care programme in rural Uganda supports changing paradigms for monitoring treatment failure in LMICs.[95] In this study, individuals infected with HIV with CD4 cell counts below 250 million cells per L or with WHO stage 3 or 4 disease were offered ART along with either clinical monitoring plus quarterly CD4 cell counts with or without viral-load testing, or clinical monitoring alone. Weekly follow-up care was provided by trained lay health-care providers in the participants' homes and, for all three treatment groups, the first response to treatment failure was to find out whether there were adherence issues and offer adherence support. All study groups performed well: 1-year mortality in the clinical monitoring group was 9%, which was lower than all but one other study in Africa. A switch to second-line drugs occurred in only 3% of participants and viral suppression at 1 year was remarkably high (90%). Individuals in the clinical monitoring group were substantially more likely to develop severe morbidity or mortality compared with clinical plus virological monitoring, immunological monitoring, or both. The investigators suggested that these groups did better because intensive adherence intervention based on CD4 cell count and viral-load test results led to high levels of resuppression. Importantly, no substantial improvement was observed by adding viral load to CD4 cell monitoring, suggesting that within a framework of regular, frequent, home-based follow-up care, CD4 cell count testing can be used effectively to monitor possible treatment failure, improve outcomes, and potentially inform decision making on the appropriate time to switch therapy.

Consequences of delayed switching

Clinical progression and the development of resistance

One of the consequences of remaining on therapy after virological failure is an increased risk of clinical progression. A substantially increased risk of disease

progression or death has been shown for HIV-infected individuals with a viral load above 10 000 copies per mL after more than 6 months on ART,[90] although this study also reported that, in some individuals, the risk of clinical progression may remain low despite a low but detectable level of HIV viraemia (501–10 000 copies per mL). Several recent studies from African clinical cohorts have reported poor outcomes associated with clinical or immunological monitoring of ART failure, including an increased risk of early morbidity and mortality.[44,96,97] However, good outcomes were seen in patients in whom ART failed who switched to second-line therapy; about 75–86% remained alive on treatment 12 months after switching regimens,[44,96,97] whereas patients remaining on failing first-line therapy were three times more likely to die.[44]

Patients remaining on therapy with low-level viraemia also have an increased risk of developing resistance.[44,83] In a retrospective analysis of the Development of AntiRetroviral Therapy in Africa RCT, there was an increased rate of NRTI resistance mutations and TAMs in individuals with a viral load above 1000 copies per mL who remained on the same treatment (table 3).[83] In patients for whom resistance data were available, a mean of 2·5 new NRTI mutations had emerged at 24–48 weeks on a failing regimen.[83]

Resistance mutations

An increasing number of studies that use patient cohort data are reporting that the prevalence of ART resistance mutations, particularly to NNRTIs and NRTIs, is increasing in LMICs (tables 3 and 4).[15,83,89,91,93,98–102] New data from a Chinese national HIV drug resistance study have shown increasing rates of viral resistance to first-line (NRTI or NNRTI) regimens from 2004–05 to 2006–07, including resistance to drugs not included in recommended first-line regimens.[91] In one study, after failure of first-line fixed-dose nevirapine, stavudine, and lamivudine, almost all individuals had lamivudine and NNRTI resistance: over 92% of patients had more than one NNRTI mutation and over 95% had more than one NRTI mutation.[98] In this setting, Tyr181Cys (Y181C) was the most common mutation, which might confer resistance to both nevirapine and efavirenz.[98] Recent data from the Argentinean resistance database showed that among 2959 individuals, 8% were fully resistant to NRTIs, and over a third were resistant to all first-generation NNRTIs.[100] In addition, several studies have shown that up to 40% of patients failing first-line stavudine–zidovudine plus lamivudine plus nevirapine–efavirenz have multiple TAMs (tables 3 and 4).[15,83,91,93,98–102] HIV-1 subtype may also play a part in development of resistance,[103–106] with implications for monitoring and treatment in these patients.

In high-income countries, guidelines suggest that resistance testing be included as standard-of-care in decision making after first virological failure.[79] In LMICs, the cost and lack of available laboratory facilities make resistance testing on virological failure challenging. As more people gain access to ART, the prevalence of resistance is likely to increase, making the decision on when to switch therapy and the choice of first-line and second-line treatment even more critical.

Effect of first-line NRTI or NNRTI resistance on second-line ART choices

Few studies from LMICs have assessed the effect of ART resistance in terms of treatment outcomes. In one study in Côte d'Ivoire,[107] immunological failure was the consequence in patients who had detectable viral loads and at least one confirmed major resistance mutation while on ART, although most patients maintained stable CD4 cell counts and stayed alive for at least 20 months. NNRTIs have a low genetic barrier to resistance and a single mutation (Lys103Asn [K103N] or Tyr188Leu [Y188L]) can lead to class-wide NNRTI resistance, and two or more mutations substantially reduce the clinical use of all approved NNRTIs.[108,109] At present, etravirine is not available in LMICs. As a result, successive use of different NNRTIs is not a viable treatment option, and the use of NNRTIs in second-line regimens is limited to those few individuals who are on triple NRTIs or first-line regimens that contain a protease inhibitor.

Development of resistance to zidovudine and stavudine and accumulation of multiple TAMs leads to treatment failure, and more importantly, compromises virological response to second-line NRTIs.[110] If an initial regimen is composed of a thymidine analogue and lamivudine, second-line therapy can be recommended to include didanosine or tenofovir. However, accumulation of multiple TAMs might result in cross-resistance and reduced virological response to NRTIs including tenofovir, didanosine, and abacavir.[89,111–113] By contrast, development of tenofovir resistance on first-line therapy may still maintain thymidine analogues as future treatment options, supporting tenofovir use in first-line ART, even though its higher cost and restricted availability in LMICs have limited its application to date.[89]

BPIs are reserved for second-line therapy in LMICs, partly due to their higher cost compared with NNRTIs, but also to maintain effective treatment options when first-line NNRTI regimens fail. Unlike NNRTIs, for which a single mutation can confer cross-class resistance, BPIs have a high genetic barrier to resistance (figure 2). Single protease mutations tend not to be associated with resistance, and accumulation of multiple major and secondary protease mutations are commonly required to confer resistance to BPIs.[108,111] In patients that were ART-naive, the use of BPIs was correlated with a decreased odds ratio for developing resistance compared to unboosted protease inhibitors

or NNRTI regimens.[114] Of note, the reduction in resistance with BPIs was observed across all levels of adherence, a factor that is critical in LMICs.[114]

Efficacy of BPI regimens

To maximise viral suppression and durability of response with second-line ART, ritonavir with BPI plus two new NRTIs is recommended (figure 1).[1] RCTs have shown that BPI regimens are effective in treatment-experienced individuals in LMICs,[115,116] and the Phidisa II Study in South Africa also showed similar efficacy with efavirenz or lopinavir and ritonavir (plus two NRTIs) in an ART-naive population.[44] Unique issues in LMICs, such as treatment interruptions due to irregular drug supply or difficulties transporting patients and delayed recognition of treatment failure with substantial consequences to resistance, should prompt consideration of the advantages of first-line BPI-containing regimens in individuals that are treatment-naive. BPIs might be favoured from a resistance perspective if availability and adherence issues exist.

Future considerations

There has been a large increase in the number of individuals infected with HIV receiving ART in LMICs, with successful early outcomes seen in many populations. Despite these findings, important issues and questions about the optimum use of ART have still to be addressed.

One limitation of our review is the difficulty in comparing data from very different sources, such as RCTs versus cohort or modelling studies, studies in high-income versus low-income countries, or studies that use government versus non-government support, rural versus urban settings, or with free versus patient-funded medication. Importantly, some of these limitations are inherent in the available studies. At present, most reports from LMICs are obtained from cohort studies, and there is a need for more RCTs to establish the best first-line and second-line regimens for use in these settings.

Programmes are needed to expand routine HIV testing, to increase individuals' awareness of their HIV status, and point-of-care CD4 cell counts should be linked with HIV antibody testing sites to determine when to initiate ART. An evolving and rapidly expanding dataset provides compelling support for earlier ART initiation with CD4 cell counts up to 500 million cells per L, to treat individuals before they reach advanced stages of disease, and potentially reduce the early mortality observed in LMICs. There is also a need to decrease the use of first-line stavudine due to the availability of newer NRTIs such as tenofovir, which may reduce toxic effects and the development of resistance.

Support needs to be built for improved monitoring of immunological and virological failure, with a focus on more affordable diagnostic tests for viral load, CD4 cell counts, and resistance, such as qualitative non-PCR-based assays for monitoring viral load, and the exploration of other prognostic serum and plasma markers for HIV. In addition, RCTs are needed to determine the long-term clinical outcomes and cost-effectiveness of virological monitoring in LMICs, and to avoid extrapolations from the results of trials done in high-income countries. Over the long term, as more individuals start to fail first-line ART, viral-load testing will become more crucial in determining early treatment failure and informing decision making on the most appropriate time to switch. Tracking of the rates of transmitted resistance in sentinel populations is crucial to determine whether an increased risk of transmitted resistance will develop with broader use of ART.

The implementation of prospective RCTs of first-line and second-line ART, strategy trials on when to switch ART, and evaluations of new diagnostic techniques will provide an outstanding opportunity to develop laboratory infrastructure for the monitoring of ART and to provide training to develop human-resource capacity. These collateral benefits will improve service delivery in LMICs, and will inform the continuous improvement of treatment guidelines. Sponsoring agencies such as PEPFAR, WHO, and the Global Fund to Fight AIDS, Tuberculosis and Malaria should consider supporting such efforts. All parties should see this as an opportunity to develop a sustainable platform for the delivery of primary health-care services in LMICs. Finally, and perhaps most importantly, despite the success of many programmes by sponsoring agencies, uncertainties remain about the source of long-term funding, particularly as the number of individuals worldwide who meet the criteria for receiving ART continues to grow.

Search strategy and selection criteria

Data for this review were identified by searches of Medline, WHO, and UNAIDS web sites, relevant conference databases, such as the Conference on Retroviruses and Opportunistic Infections and the International AIDS Society, and references from relevant articles. The date limits of the searches were January, 1994, to February, 2009. Search terms included "HIV", "AIDS", "resource-limited setting", "early mortality", "antiretroviral therapy", "first-line ART", "treatment failure", "resistance", "toxicity", "second-line ART", "switching", and "monitoring". Only papers published in English were reviewed.

Contributors

JAB was involved in the development of the overall concept and structure of this article, searching for and selecting source material, and reviewing, writing, and editing of the paper. JFS provided critical interpretation of the selected references, and reviewed and approved the paper.

Conflicts of interest

JAB has received research support, consulting fees, and speaking honoraria from Abbott Laboratories, and consulting fees from Pfizer, Merck, and Argos Laboratories. JFS declares no conflicts of interest.

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