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Prevention and treatment of human immunodeficiency virus/acquired immunodeficiency syndrome in resource-limited settings

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Abstract Strategies for confronting the epidemic of human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) have included a range of different approaches that focus on prevention and treatment. However, debate persists over what levels of emphasis are appropriate for the different components of the global response. This paper presents an overview of this debate and briefly summarizes the evidence on a range of interventions designed to prevent the spread of HIV infection, paying particular attention to voluntary counselling and testing, treatment for sexually transmitted infections and prevention of mother-to-child transmission. We also review the experience with antiretroviral therapy to date in terms of response rates and survival rates, adherence, drug resistance, behavioural change and epidemiological impact. Although various studies have identified strategies with proven effectiveness in reducing the risks of HIV infection and AIDS mortality, considerable uncertainties remain. Successful integration of treatment and prevention of HIV/AIDS will require a balanced approach and rigorous monitoring of the impact of programmes in terms of both individual and population outcomes.

Keywords HIV infections/prevention and control/drug therapy; Acquired immunodeficiency syndrome/prevention and control/drug therapy; Anti-retroviral agents/therapeutic use; Antiretroviral therapy, Highly active/utilization; Counseling; Disease transmission, Vertical/prevention and control; Sexually transmitted diseases/prevention and control; Treatment outcome; Evidence-based medicine; Developing countries (*source: MeSH, NLM*).

Mots clés Infection à VIH/prévention et contrôle/chimiothérapie; SIDA/prévention et contrôle/chimiothérapie; Agents antirétroviraux/usage thérapeutique; Thérapie antirétrovirale hautement active/utilisation; Conseil; Transmission verticale maladie/prévention et contrôle; Maladies sexuellement transmissibles/prévention et contrôle; Evaluation résultats traitement; Médecine factuelle; Pays en développement (*source: MeSH, INSERM*).

Palabras clave Infecciones por VIH/prevención y control/quimioterapia; Síndrome de inmunodeficiencia adquirida/prevención y control/quimioterapia; Agentes antirretrovirales/uso terapéutico Terapia antirretroviral altamente activa/utilización; Consejo; Transmisión vertical de enfermedad/prevención y control; Enfermedades sexualmente transmisibles/prevención y control; Resultado del tratamiento; Medicina basada en evidencia; Países en desarrollo (*fuente: DeCS, BIREME*).

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Introduction

Strategies for confronting the epidemic of human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) have included a range of approaches that focus on prevention and treatment. However, debate persists over the degree of emphasis appropriate to the different components of the global response to the pandemic. Outside wealthy countries, most of the public health interventions for HIV/AIDS have concentrated on prevention. More recently, expansion of antiretroviral therapy (ART) to resource-limited settings has gained prominence as a topic of international debates on HIV/AIDS. In December 2003, WHO launched an initiative to scale up ART delivery to those in need to meet the "3 by 5" target of 3 million people receiving treatment by the end of 2005.

In this paper, in the context of resource-limited settings, we summarize the debate over ART expansion and the evidence on the effectiveness of prevention strategies, especially

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those interventions likely to be most prominent in efforts to integrate prevention and treatment. We then review the experience gained thus far with ART in resource-limited settings and consider areas of research that may advance the global response to HIV/AIDS.

Evolving paradigms

Efforts to reduce HIV transmission have varied in focus as competing prevention paradigms have captured the interest of decision-makers and funding agencies. Early in the epidemic, an emphasis on "core groups" of transmitters led to prevention efforts being directed towards female sex workers, men who have sex with men (MSM) and intravenous drug users (*1*). As attention has broadened to include risk behaviours in the wider community, particularly in generalized epidemics such as that in sub-Saharan Africa, more recent debates have revolved around the scope and focus of prevention strategies. The central role of condoms in controlling HIV has been questioned by proponents of the "ABC" approach, which gives priority to "A" (abstinence) and "B" (being faithful) over "C" (condoms) (*2*). Arguments, put forward primarily by the US Government, for an abstinence-only educational message have been repudiated on scientific grounds, and opponents have cautioned against politicizing school-based education strategies (*3*).

Although the importance of risk groups and risk behaviour is widely recognized, frustration over limited progress in reducing the incidence of HIV worldwide has bolstered the view that social vulnerability and stigma may hinder the effective implementation of prevention programmes. Calls for treatment as a means to enhance prevention, however, have been accompanied by contentious international debates over scaling up ART in resource-poor settings.

The reservations about the expansion of ART have revolved around the practical challenges of implementing treatment programmes and the high costs of the drugs. In consideration of the severe constraints on human resources in many developing countries and the limited capacity to monitor CD4 cell counts and viral loads, those urging caution in scaling up ART have pointed out that inadequate oversight and care could lead to negligible improvements in survival coupled with the development of drug resistance (*4*, *5*). Opponents of ART expansion have frequently used arguments related to cost-effectiveness, suggesting that greater health gains could be realized for a given financial investment if it were devoted to prevention rather than treatment. For example, one study estimated that ART would cost US$ 1100–1800 per disability-adjusted life year (DALY) averted, whereas preventive interventions such as voluntary counselling and testing (VCT) or condom distribution would cost US$ 18–22 and US$ 1–99 per DALY averted, respectively (*6*). Another study concluded that the cost of treatment was at least 28 times higher per DALY averted than that of average prevention programmes (*7*). Although pressure from advocacy groups and the advent of generic drugs have reduced the costs of antiretrovirals precipitously, from more than US$ 10 000 to as low as US$ 140 per patient-year (*8*), some cost-effectiveness differential between prevention and treatment is likely to persist (*6*).

Proponents of ART scale-up in developing countries have invoked human rights arguments (*9*) and challenged the relevance of cost-effectiveness (*10*). Some experts, citing a failure of past efforts to control the epidemic, expect widespread ART to reduce stigma, increase uptake of voluntary testing, enhance community acceptance of other important prevention programmes, and to contribute directly to interrupting transmission by suppressing viral load and providing new opportunities for counselling on safe sexual behaviour (*11*, *12*). Critics of cost-effectiveness studies point to a range of health, social and economic benefits that are not captured in these analyses — scaling up ART could strengthen the infrastructure for basic health-care delivery and increase the total amount of money available for health rather than drawing resources away from other health programmes (*11*, *13*). Others have noted that treatment programmes could aid development efforts by boosting economic productivity and limiting the social disruption caused by the HIV/AIDS epidemic (*14*).

Evidence on effectiveness of prevention

Grassly et al. (*15*) presented a useful framework for assessing the effectiveness of prevention within particular epidemiological contexts. They noted that most studies had evaluated intermediate indicators such as changes in behaviour (e.g. condom use, reduction in the number of sexual partners and treatment-seeking for sexually transmitted infections (STIs)) rather than epidemiological outcomes such as changes in incidence or mortality. Often, these studies combined multiple interventions, which complicated the evaluation of the contributions made by the separate components to the overall observed benefits. Furthermore, because the studies were conducted in specific controlled settings, the generalizability and replicability of successful prevention trials is not guaranteed. Despite these limitations, however, an examination of the existing evidence indicates that a number of different intervention strategies can be effective in reducing HIV risk behaviours (*6*, *15–19*) (Table 1).

As interest in the potential for integrated prevention and treatment efforts increases, three preventive interventions may be particularly relevant as components of a comprehensive response to the epidemic: VCT, treatment of STIs and prevention of mother-to-child transmission (pMTCT).

Voluntary counselling and testing

Voluntary counselling and testing combines confidential provision of information on serostatus, counselling for seropositive individuals and education on reducing the risks of transmission. Where antiretrovirals are available, VCT can also identify candidates for pMTCT or AIDS treatment. A large randomized trial in Kenya, Trinidad and Tobago, and the United Republic of Tanzania measured changes in self-reported sexual behaviour among individuals returning for a first follow-up session (82%, $n = 2550$). Those who had received both counselling and testing reported greater reductions in unprotected sex with non-primary partners than those who had received health information without serostatus results (reductions of 35% and 39% for men and women, respectively, in the VCT arm, versus 13% and 17% in the control arm). The reductions in risk were greater among seropositive than seronegative individuals (*20*). A cost-effectiveness analysis linked to this study estimated that VCT would cost US$ 13–18 per DALY averted (making the intervention highly attractive when assessed using typical benchmarks) and indicated that VCT is most cost-effective in high-prevalence settings and when administered to couples rather than to individuals (*21*). Although these and similar results obtained elsewhere are encouraging, less optimistic outcomes have occasionally been reported (*22*, *23*). Moreover, although VCT has been shown to reduce sexual behaviour among participants, the

Table 1. **Findings from selected reviews of effectiveness studies on interventions to prevent human immunodeficiency virus/acquired immunodeficiency syndrome in resource-limited settings**

Study	Outcomes measured	Interventions	Findings
Bollinger et al., 2004 (*16*)	Behaviour	*Risk-group specific*: FSW[a], out-of-school youth, STI[b], IDU[c], MSM[d] *General*: mass media, SBE[e], VCT[f], condom promotion, community mobilization, work-based education	Lack of control groups limits strength of many studies. Targeted interventions for FSW very effective. Little evaluation of youth interventions, work-based education, IDU or MSM
Walker, 2003 (*17*)	Cost-effectiveness	*Risk-group specific*: FSW and clients, STI, IDU, pMTCT[g] *General*: mass media, SBE, VCT, condom promotion, microbicides	Not enough data to generalize cost-effectiveness results across settings. Several interventions (FSW, STI, IDU, pMTCT, condom promotion, VCT) may be cost-effective. Limited data suggest SBE programmes are expensive. Little evidence on mass media and microbicides
Creese et al., 2002 (*6*)	Cost-effectiveness	*Risk-group specific*: FSW, STI, pMTCT *General*: VCT	Several interventions may cost less than US$ 75/DALY[h] gained, including FSW, STI, pMTCT and VCT
Grassly et al., 2001 (*15*)	Behaviour, knowledge and beliefs	*Risk-group specific*: clients of FSW, STI, pMTCT *General*: SBE, VCT	Only randomized controlled trials of pMTCT demonstrate effect on HIV incidence. Some evidence of effectiveness for clients of FSW, SBE, STI and VCT
Plummer et al., 2001 (*18*)	HIV incidence, behaviour, knowledge and beliefs	*Risk-group specific*: FSW and clients, STI, IDU, MSM, pMTCT *General*: mass media, SBE, VCT, microbicides, male circumcision	Strong evidence for FSW and clients, MSM and pMTCT. Some evidence for STI treatment and VCT. Limited evidence for SBE, mass media and microbicides. IDU and MSM effective in developed world but few studies in resource-poor settings. Male circumcision promising
Merson et al., 2000 (*19*)	HIV incidence, behaviour, knowledge and beliefs	*Risk-group specific*: FSW and clients, STI, IDU *General*: SBE, VCT, community education, condom distribution	FSW and clients very effective. VCT effective for HIV-positives. Few studies of IDU, MSM, SBE or community education. Mixed evidence on condom distribution

[a] FSW = female sex workers.
[b] STI = Treatment for other sexually transmitted infection.
[c] IDU = intravenous drug users.
[d] MSM = men who have sex with men.
[e] SBE = school-based education.
[f] VCT = voluntary counselling and testing.
[g] pMTCT = prevention of mother-to-child transmission.
[h] DALY = disability-adjusted life year.

overall effectiveness of VCT programmes will depend on levels of uptake, which may be depressed by stigma and limited access to treatment (*24*).

Treatment of sexually transmitted infections

Because the presence of another STI has been shown to increase both susceptibility to and transmissibility of HIV, and because most STIs may be cured by antibiotics, treatment of STIs has been considered as a potential HIV prevention measure. The results from three large community-based randomized controlled trials in sub-Saharan Africa provided mixed evidence on whether STI treatment could reduce the incidence of HIV in a community. In Mwanza, United Republic of Tanzania, the incidence of HIV was 40% lower in the intervention arm (using syndromic STI management) than in the control arm of the trial despite no change in sexual behaviour being reported and, surprisingly, despite no significant reductions in prevalence of STIs in the intervention arm (*25*). In Rakai, Uganda, a trial of mass STI treatment, supplemented by syndromic management in both the intervention and control arms, found no significant difference in HIV incidence, despite significant reductions in the prevalence of syphilis and non-ulcerative infections in the intervention arm (*26*). A more recent study in Masaka, Uganda compared behavioural interventions, with or without syndromic STI management, to routine government health programmes and found greater condom use and lower prevalence of STIs in the intervention arms, but the incidence of HIV was not significantly different from that in controls (*27*).

Attempts to explain the apparent discrepancy between the findings of the Mwanza study and those of the two studies in Uganda have pointed to the higher baseline prevalence of non-ulcerative infections and syphilis in Mwanza than in Rakai and Masaka (*28*); the lesser importance of STI in advanced epidemics such as the one in Rakai (*29*); the relative importance of non-treatable HSV-2 as a cofactor (*29*); and previous reductions in sexual behaviour in Uganda (*30*). Although the three studies give somewhat ambiguous support for the direct impacts of STI treatment on HIV incidence, the biological links between STI and HIV infectivity, combined with the contact that STI treatment encourages between high-risk individuals and public health services, justify continued consideration of a potential role for STI treatment in an integrated response to HIV/AIDS.

Prevention of mother-to-child transmission

An estimated 15–40% of infants born to mothers infected with HIV-1 will become infected themselves (*31*), and high maternal viral load is the major risk factor for transmission (*32*). The ACTG 076 study in France and the United States demonstrated that zidovudine could reduce the probability of perinatal transmission of HIV by almost 70% (*31*), but used relatively expensive and complex protocols typical of high-income countries (oral doses 5 times daily during pregnancy, intravenous administration to the mother intrapartum, and oral doses 4 times daily to the newborn for 6 weeks after birth). For resource-limited settings, there has been interest in the potential impact of short-course regimens. In a study in Thailand, twice-daily doses of zidovudine from 36 weeks of gestation and every 3 hours during labour reduced transmission risks by 50% if the mother did not breastfeed her infant (*33*). The HIVNET 012 trial in Uganda found a relative transmission risk (at 14–16 weeks) of 0.47 (95% confidence interval (CI) = 0.20–0.64) for a single-dose of nevirapine during labour followed by a single dose given to the infant within 72 hours of birth, when compared with multiple doses of zidovudine administered during labour followed by twice-daily doses given to the infant for 7 days after birth (*34*). These risk reductions were sustained through 18 months (15.7% (95% CI = 11.5–19.8%) for nevirapine versus 25.8% (95% CI = 20.7–30.8%) for zidovudine) (*35*). The Petra study in South Africa, Uganda and the United Republic of Tanzania, compared zidovudine plus lamivudine in three different protocols (prepartum, intrapartum and postpartum; intrapartum and postpartum; and intrapartum alone) and found relative risks of HIV infection or death (at week 6 postpartum) of 0.39 (95% CI = 0.24–0.64), 0.64 (95% CI = 0.42–0.97) and 0.97 (95% CI = 0.68–1.38) for the three protocols, respectively, compared to placebo treatment. The convergence of infection levels in the treatment and control arms of the study by the time the infants were 18 months old suggests risks associated with breastfeeding (*36*).

Taken together, these studies indicate that short courses of antiretroviral therapy can reduce perinatal transmission by approximately 50%. Based on these effectiveness data, subsequent analyses have concluded that pMTCT is cost effective; the costs are of the order of US$ 5–274 per DALY averted, depending on the protocol and coverage level (*37*).

Prevention programmes in practice

Despite accumulated evidence that interventions aimed at preventing infection can be effective in trial settings, examples of their successful implementation at the national level remain scarce. It is estimated that globally only 5% of pregnant women attending antenatal clinics have access to pMTCT services; 12% of individuals who want testing have access to VCT; and 42% of people at risk of acquiring HIV through unprotected sex can obtain condoms (*38*).

Thailand and Uganda are among a small number of developing countries notable for having achieved significant reductions in HIV prevalence. In Thailand, efforts to reduce transmission in the commercial sex industry served as a focal point in a more general public campaign centered on a "100% Condom Programme" using the mass media and an established network of STI treatment clinics for education about HIV/AIDS and distribution of free condoms (*39*). Reductions in the prevalence of HIV in Thai army recruits (3.7% in 1993 compared with 1.9% in 1997) and pregnant women (2.4% in 1995 compared with 1.7% in 1997) accompanied decreases in risky sexual behaviour (increases in condom use among brothel-based sex workers from 87% to 97% and among other sex workers from 56% to 89% between 1993 and 1996; and decreases in extramarital and commercial sex from 22% to 10% between 1990 and 1997) (*40*).

In Uganda, which is often cited for its comprehensive, multisectoral response to HIV/AIDS (*41*), attributing epidemiological changes to specific interventions is difficult. Surveillance data from antenatal clinics show reductions in prevalence of at least 50% since the early 1990s; in Kampala, HIV prevalence among pregnant women dropped from 29% in 1992 to 11% in 2000, while in rural areas the median prevalence decreased from 13% to 6% (*42*). Debates persist over the causes of the reductions in prevalence observed in Uganda (for example, the relative importance of reduction in the number of sexual partners versus condom use), but the government-sponsored public awareness campaigns on HIV/AIDS risks that were run earlier in the epidemic are likely to be an underlying factor (*41*).

Impact of antiretroviral therapy to date

The primary end-points in studies of the effectiveness of ART have been the reduction in viral load and the increase in CD4 cell count; both are correlated with increased survival rates. Reducing viral load inhibits disease progression and reduces the probability of transmitting infection. Increasing the CD4 count bolsters the ability of the immune system to fight the diseases to which people with AIDS have increased susceptibility. In developed countries, controlled trials of highly active antiretroviral therapy (HAART) — which typically combines two nucleoside reverse transcriptase inhibitors (NRTIs) with a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor (NNRTI) — have shown reductions in viral load to undetectable levels and increases in CD4 counts among patients who had CD4 levels above 200 cells/μl at the initiation of therapy (*43*). No studies in developing countries have assessed the optimal timing for initiation of treatment, but experience in high-income countries suggests that therapy should be started at CD4 counts of 200–350 cells per μl to maximize patient survival while avoiding unnecessary exposure to ART medications and the resulting side-effects (*44*).

Treatment response and survival

Recent clinical studies of ART in resource-poor settings have demonstrated virological, immunological and survival benefits comparable to those reported in the industrialized world (*45–52*) (Table 2). For treatment-naive individuals, median gains in CD4 cell counts ranged from 75–245 per μl, and reductions in viral load ranged from 1.6–3.3 log copies/ml while on HAART. Two-year survival may approach 80%. Of particular interest is the recently published report of a trial in Cameroon of a fixed-dose generic HAART regimen (combining nevirapine, stavudine and lamivudine), in which most of the study participants (92%) already had AIDS. After 24 weeks, 80% of patients had an undetectable viral load, and the probability of surviving and being free of new AIDS-defining events was 85% (*46*).

Adherence

In practice, replication of the gains attained in controlled clinical trials depends critically on levels of adherence. At the individual level, adherence is an important determinant of survival, and at

Table 2. **Results from selected studies of antiretroviral therapy for human immunodeficiency virus/acquired immunodeficiency syndrome in resource-limited settings**[a]

Study	Country	*n*	Median[b] follow-up (months)	Median[b] CD4 count at baseline ($\times 10^6$ cells/l)	Median[b] increase in CD4 ($\times 10^6$ cells/l)	Percentage with undetectable viral load[c]	Survival rate
Coetzee et al., 2004 (*45*)	South Africa	287	14	43	+288	70	0.86
Laurent et al., 2004 (*46*)	Cameroon	60	6	118	+83	80	0.85
Djomand et al., 2003 (*47*)[d]	Côte d'Ivoire	276	6	182	+100	50 (<200 copies/ml)	0.84
Kumarasamy et al., 2003 (*48*)	India	333	7 (mean)	171	+192[e]		0.98
Landman et al., 2003 (*49*)	Senegal	40	15	162	+199 (mean)	95	No reported deaths
Ungsedhapand et al., 2003 (*50*)[f]	Thailand	53	11	331 (mean)	+105 (mean)	69	No reported deaths
Laurent et al., 2002 (*51*)	Senegal	58	20	109	+180	59	0.82
Weidle et al., 2002 (*52*)[d]	Uganda	204	12[g]	78	+80	45	0.82 (baseline CD4 $\geqslant$ 50) 0.67 (baseline CD4 < 50)

[a] Some figures have been estimated indirectly where exact figures were not provided in text or tables. Details are available from the authors.
[b] Except where indicated.
[c] Plasma HIV-1 RNA levels below 400 or 500 copies/ml except where indicated.
[d] Results reported for highly active antiretroviral therapy (HAART) only where other regimens were also included, except for survival rate in Djomand et al. (*47*) which is reported for HAART and treatment with two nucleoside reverse transcriptase inhibitors combined.
[e] Increase reported for those patients followed up for at least 12 months ($n = 75$).
[f] Results reported for triple nucleoside reverse transcriptase inhibitor regimen.
[g] The authors reported the median observation time as 94 days, but estimated immunological and survival results at 1 year.

the population level, sustained reductions in viral load are essential for reducing transmission. Poor adherence is also linked to the development of drug resistance, which can compromise response to therapy and spread refractory infections (*53*).

Some authors have suggested that adherence is particularly challenging in resource-poor settings where antiretrovirals may be used without appropriate counselling or tools for monitoring outcomes (*5*). Although comparisons between studies must be made with caution because of varying definitions and modes of ascertaining adherence, reports of adherence levels above 90% in China (*54*), Senegal (*55*) and South Africa (*56*) are encouraging and compare favourably to those reported from Europe and North America, where adherence is around 70% (*57*). Drug costs are noted as an important determinant of non-adherence (*55*); a study in Botswana estimated that adherence would rise from 54% to 74% if drugs were provided free of charge (*58*). As ART coverage expands in developing countries, a broad spectrum of drugs will be needed to provide effective alternatives for the treatment of those patients who discontinue their regimens due to drug toxicity and adverse events (*59*).

Drug resistance

Some level of drug resistance is likely to occur in any population in which ART is used, and even at high rates of adherence (>90%) resistance can occur in patients with incomplete viral suppression (*60*). At the population level, resistance can be monitored by assays in newly infected, treatment-naive individuals. In the United States, the prevalence of drug resistance in this group increased from 5% before 1996 to 10–22% by 2000. This was comparable to rates reported in Europe and much higher than levels reported in Brazil (*57*, *61*). With the exception of Brazil, studies of resistance in the developing world have been limited to monitoring patients over the course of treatment. A study in Senegal found that treatment-naive individuals were less likely than previously treated individuals to develop resistant strains after 18 months of therapy (11.8% versus 41.7%) (*62*), and in Thailand, the rates of resistance among patients receiving HAART were 12–48% across different drug classes (*63*). A study in Uganda found higher rates of resistance in patients treated with dual therapy than in those who received HAART (56% and 36% for patients treated with two NRTIs and HAART, respectively) (*64*).

Behavioural response

The introduction of effective AIDS treatment in Europe and the United States has had mixed effects on sexual behaviour. The Swiss HIV Cohort Study ($n = 4723$) found no association between unsafe sex and optimal viral suppression for individuals on HAART (*65*). However, studies of MSM reported increases in unsafe sex with reductions in viral load (*66*) and increases in prevalence of STIs among those receiving HAART (*67*). Another concern is the possibility of increased risky sexual behaviour among seronegative individuals in response to the availability of ART. Sexual disinhibition has been most thoroughly documented via increasing rates of gonorrhoea and

unprotected sex among MSM in San Francisco, USA (*68*). The only published study to date to address the sexual behaviour of ART patients in resource-limited settings presents more optimistic results. In Côte d'Ivoire, patients receiving ART were less likely to engage in unprotected sex than individuals not receiving therapy (univariate odds ratio (OR) 0.44 (95% CI = 0.26–0.74), multivariate OR 0.52 (95% CI = 0.29–0.93)) (*69*). The population-level behavioural response in resource-poor settings has yet to be determined.

Epidemiological impact

In high-income countries, the development and evolution of antiretroviral drugs in the past decade has led to dramatic reductions in AIDS-related mortality. In Europe and North America, the hazard ratio for death in 2001 compared to 1997 was 0.16, and estimated 12-year survival for HIV seroconverters in 2001 was well over 80% (*70*).

In the developing world, where it was estimated that only 400 000 of the 6 million people in need of ART had access to this treatment at the beginning of 2004 (*71*), there is little empirical basis on which to gauge the epidemiological impact in areas where scale-up has already begun. The success of widespread AIDS treatment must ultimately be assessed in terms of reductions in both AIDS mortality and HIV incidence. As the principal example for middle-income countries, Brazil's programme of universal free access to ART has produced increases in median survival times from 18 months for patients diagnosed in 1995 to 58 months for those diagnosed in 1996 when HAART was introduced (*72*). Experts predict that initial application of HAART in resource-limited countries may yield more limited survival gains on average (approximately 3 years) due to the advanced stage of disease of those eligible for treatment and lack of capacity to monitor CD4 count and viral load and to treat opportunistic infections (*73*). Measuring the incidence of HIV at the population level is challenging, and the impact of ART on the spread of infection remains uncertain.

Looking ahead

The research agenda on effectiveness of prevention and treatment for HIV/AIDS includes a number of promising avenues. Development of microbicides for the protection of women and investigation of the protective effects of male circumcision against HIV transmission are examples of current prevention research. Rapid tests for HIV serostatus are likely to increase uptake of VCT and pMTCT programmes. Cheaper diagnostic tools for monitoring CD4 cell counts and viral loads would allow clinicians in low-income countries to initiate treatment earlier and to prescribe optimal drug regimens, which will improve outcomes (*74*). Drug combinations that reduce the number of pills and frequency of dosing required, drugs with fewer side-effects and structured interruptions in therapy could all increase patient adherence.

Positioning ART within a comprehensive approach to HIV/AIDS that integrates prevention and treatment will be facilitated by selecting entry points to ART that can provide enhanced prevention services. The "MTCT-Plus" programmes, which aim to provide lifetime treatment to mothers receiving antiretrovirals to prevent neonatal transmission, offer an existing model of intersection between treatment and prevention services (*75*). Expanding coverage of STI treatment could help identify candidates for ART within high-risk populations and potentially reduce the spread of HIV infection by mitigating transmission cofactors. Another option to extend the reach of VCT and treatment would be to build on tuberculosis control programmes (*10*). Although availability of treatment is expected to increase uptake of VCT, aggressive community education may be needed in some contexts (*76*).

Integration of prevention and treatment in practice will require adequate and sustained funding for both sets of activities, and rigorous monitoring and surveillance of the impact of treatment in terms of both clinical results and broader epidemiological consequences. Studies should be initiated at the outset of ART expansion to determine the effect of treatment availability on the sexual behaviour of the individual patients and of the community, as well as on the uptake of prevention programmes such as VCT. Successful expansion of treatment programmes will offer unique opportunities to strengthen monitoring and evaluation capacity through leveraging of the sustained resource commitments that will be needed to deliver effective ART. Indicators of success for the "3 by 5" initiative should go beyond the defining goal of extending treatment to 3 million people in need, to include substantiation of reductions not only in AIDS mortality, but also in the spread of new infections in the community.

This review of the existing evidence on prevention and treatment in HIV/AIDS epidemics points to certain strategies with proven effectiveness, but also highlights those areas where uncertainty persists. Global and national policy responses to the HIV pandemic must proceed before all these uncertainties are resolved. However, efforts to expand the evidence base for these policies must continue in parallel with their implementation, and progress and directions in the scale-up of ART delivery should be re-evaluated regularly as new evidence emerges. ■

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Résumé

Prévention et traitement du VIH/SIDA dans les pays à ressources limitées

Parmi les stratégies qui ont été opposées à l'épidémie de VIH/SIDA, on peut mentionner diverses approches axées sur la prévention et le traitement. Cependant, les débats se poursuivent sur l'importance à accorder aux différentes composantes de la réponse mondiale. Le présent article présente une synthèse de ces débats et résume brièvement les données relatives à une série d'interventions destinées à prévenir la propagation de l'infection à VIH, en accordant une attention particulière au conseil et au dépistage volontaires, au traitement des infections sexuellement transmissibles et à la prévention de la transmission mère-enfant. Les auteurs examinent également l'expérience acquise à ce jour avec les traitements antirétroviraux en termes de taux de réponse et de survie, d'observance du traitement, de résistance médicamenteuse, de changement des comportements et d'impact

épidémiologique. Bien que diverses études aient identifié des stratégies offrant une efficacité prouvée dans la réduction des risques d'infection par le VIH et de mortalité par le SIDA, des incertitudes considérables subsistent. Une intégration réussie du traitement et de la prévention du VIH/SIDA suppose une approche équilibrée et une surveillance rigoureuse de l'impact des programmes en matière de résultats individuels et collectifs.

Resumen

Prevención y tratamiento del VIH/SIDA en entornos con recursos limitados

Las estrategias empleadas para hacer frente a la epidemia de virus de la inmunodeficiencia humana/síndrome de inmunodeficiencia adquirida (VIH/SIDA) se han servido de diferentes enfoques centrados en la prevención y el tratamiento. Sin embargo, persiste el debate sobre la importancia que debería atribuirse a los diferentes componentes de la respuesta mundial. En el presente artículo se ofrece un panorama de este debate y se resume brevemente la evidencia disponible sobre varias intervenciones diseñadas para prevenir la propagación de la infección por el VIH, prestando especial atención al asesoramiento y las pruebas voluntarias, el tratamiento de las infecciones de transmisión sexual y la prevención de la transmisión de la madre al niño. También examinamos la experiencia acumulada con la terapia antirretroviral hasta la fecha en cuanto a las tasas de respuesta y las tasas de supervivencia, la observancia, la farmacorresistencia, los cambios de comportamiento y el impacto epidemiológico. Aunque diversos estudios han identificado estrategias de demostrada eficacia para reducir el riesgo de infección por VIH y la mortalidad por SIDA, sigue habiendo bastantes interrogantes. Para integrar con éxito el tratamiento y la prevención de la infección por VIH/SIDA se requerirá un enfoque equilibrado y una vigilancia rigurosa del impacto de los programas en términos de resultados tanto individuales como poblacionales.

ملخص

الوقاية من الإيدز والعدوى بفيروسه ومعالجته في المواقع المحدودة الدخل

الملخص: تتضمن استراتيجية مكافحة الإيدز والعدوى بفيروسه طائفةً من الأساليب التي تركّز على الوقاية والمعالجة؛ ورغم ذلك، يتواصل الحوار حول مستويات التركيز الملائمة لكل مقوِّم من مقوِّمات الاستجابة العالمية. وتستعرض هذه الورقة الخطوط العريضة في هذا الحوار وتلخص البيِّنات حول طائفة من التدخُّلات التي صممت للوقاية من انتشار العدوى بفيروس الإيدز، مع إيلاء اهتمام خاص للتوعية الطوعية والاختبار الطوعي ومعالجة الالتهابات المنقولة جنسياً والوقاية من سراية الفيروس من الأم لطفلها. كما تستعرض هذه الورقة الخبرات الراهنة في المعالجة بالأدوية المضادة للفيروسات القهقرية المسبِّبة للإيدز من حيث معدلات الاستجابة ومعدلات البقاء على قيد الحياة، والامتثال للمعالجة، والمقاومة للأدوية، والتغيرات السلوكية والتأثيرات الإبيديميولوجية (الوبائية). ورغم وجود العديد من الدراسات التي حدَّدت استراتيجيات ذات كفاءة مثبتة في تخفيض أخطار العدوى بفيروس الإيدز ومعدلات الوفيات الناجمة عن الإيدز فإن قدراً كبيراً من عدم الثقة لايزال موجوداً، وسيتطلب التكامل بين المعالجة والوقاية من الإيدز ومن العدوى بفيروسه أسلوباً يتَّسم بالتوازن كما يكفل الرصد الصارم لتأثير البرامج من حيث تأثيرها على الحصائل التي يجنيها الأفراد والمجتمعات.

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