

HIV-1/AIDS and the control of other infectious diseases in Africa

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The effect of HIV-1 on other infectious diseases in Africa is an increasing public health concern. In this review, we describe the role that three major infectious diseases—malaria, sexually transmitted diseases (STDs), and tuberculosis—have had in the HIV-1 epidemic. The high prevalence of untreated STD infections has been a major factor facilitating the spread of HIV-1 in Africa; with the synergistic interaction between HIV-1 transmission and genital herpes being of especial concern for control of both diseases. Increased susceptibility to tuberculosis after infection with HIV-1 has led to a rising incidence and threat of increased transmission of tuberculosis. Clinical malaria occurs with an increased frequency and severity in HIV-1-infected individuals, especially during pregnancy. As with tuberculosis, STDs, and other communicable HIV-1-associated diseases, the net effect of HIV-1 might include increased rates of malaria transmission across communities. In addition to enhancing access to HIV-1 prevention and care, public health surveillance and control programmes should be greatly intensified to cope with the new realities of infectious disease control in Africa.

The epidemic of HIV-1 infection has not arisen in isolation, but within the context of pre-existing difficulties in disease control. These difficulties are especially evident in Africa, where few resources and poor access to care have maintained an environment in which many infectious diseases persist at high rates. HIV-1 has become a major endemic infection in Africa, with an unusually high potential to interact with other disorders, both through the generation of many immunosuppressed individuals and because its own infectivity and clinical course is altered by other infections (figure 1).

These interactions affect the control of HIV-1 and associated diseases in several ways. In areas of high HIV-1 prevalence, the incidence of HIV-1-associated infections will also be high, as will mortality rates, since case-fatality rates tend to be higher for HIV-1-positive than for HIV-1 negative individuals.¹⁻⁷ Transmission rates of contagious HIV-1-associated infections will rise, especially if per-case infectivity is also increased by co-infection with HIV-1. At the cellular level, increased viral replication with longlasting perturbations in cytokines and plasma viral load can follow HIV-1-associated infections, possibly leading to accelerated^{8,9} HIV-1 progression in regions with intense exposure to infections,⁹ though data are conflicting.⁸ Finally, HIV-1 infectivity can be increased by other infections, especially sexually transmitted diseases (STDs),¹⁰⁻¹⁴ leading to high rates of HIV-1 transmission in communities with high prevalence of other diseases. Increased transmission could also theoretically occur with all other infections, since these result in a transient burst of

HIV-1 replication, and viral loads in plasma correlate with HIV-1 infectivity.¹⁵

The net effect of these interactions varies considerably. The main effect of STDs has been a rise in HIV-1 transmission,¹⁰⁻¹⁴ whereas the most obvious interaction of HIV-1 with tuberculosis has been to increase the burden of an already major cause of morbidity and mortality.^{16,17} Diseases that were once rare such as cryptococcosis have become common, and HIV-1-associated infections the main causes of admissions to hospital and death in many African countries, with most morbidity and mortality caused by preventable infections such as *Mycobacterium tuberculosis*, *Salmonella* spp, other enteric pathogens, bacterial pneumonia, and malaria.¹⁻⁷

A further major concern is the potential effect of HIV-1 on transmission rates and dynamics of HIV-1-associated infections that are directly or indirectly transmitted from person to person. In this respect, the HIV-1 epidemic could compound an already heavy public health burden and threaten the health and survival of all Africans, irrespective of HIV-1 status. We focus here on the role that three major communicable diseases—malaria, STDs, and tuberculosis—have had in the HIV-1 epidemic, and on prospects for improving their control.

Malaria

In sub-Saharan Africa, the HIV-1 epidemic has been superimposed on the longstanding malaria pandemic in which *Plasmodium falciparum* malaria is consistently one of the top three causes of infant and child mortality. WHO estimates that malaria contributes to more than 300 million infections and more than 1 million deaths of children every year, almost all in sub-Saharan Africa.¹⁸ Although driven by very different transmission mechanisms and dynamics, wide geographical overlap and high prevalence of HIV-1 and malaria infections mean that even small interactions could lead to substantial population effects.^{19,20}

Search strategy

We did literature reviews using relevant Medline search terms, screened articles for relevance, and reviewed references. Because of space restrictions, review articles have been cited in place of original manuscripts where possible. References are not intended to provide a comprehensive listing, but were chosen to best highlight the important points.

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	Incident cases per year (millions)		
	Men	Women	Total
Syphilis	2.1	1.7	3.8
<i>C trachomatis</i>	7.6	8.2	15.9
<i>N gonorrhoeae</i>	8.2	8.8	17.0
<i>T vaginalis</i>	16.2	15.9	32.1
Total	34.1	34.6	68.7

C trachomatis=Chlamydia trachomatis. *N gonorrhoeae*=Neisseria gonorrhoeae.
T vaginalis=Trichomonas vaginalis.

Table 1: Estimated incidence of curable STDs in people aged 15–49 years in sub-Saharan Africa⁵⁰

pyrimethamine might further the development of resistance to co-trimoxazole by other pathogens, such as *Streptococcus pneumoniae*.³⁹ Co-trimoxazole is already widely used in sub-Saharan Africa as part of integrated management of childhood illnesses in presumptive treatment of pneumonia.^{39,40} The extent to which the considerable short-term benefits from prophylactic use of co-trimoxazole for HIV-1/AIDS outweigh the long-term risks of increasing rates of resistance to both antifolates in malaria and other common infections remains to be determined.^{1,2,40} The effectiveness of these drugs should be carefully monitored in HIV-1 and malaria control programmes.

Chloroquine, the most widely used antimalarial drug in Africa, has in-vitro anti-HIV-1 activity.^{41,42} In HIV-1-infected adults, the metabolite hydroxychloroquine can reduce HIV-1 replication.⁴² Because the site of action of chloroquine differs from other commonly used antiretroviral agents, the drug is being assessed for inclusion in combination therapy for treatment of HIV-1 infection and prevention of post-partum mother-to-child transmission in breastfeeding populations in resource-poor settings.⁴¹ Prospective studies addressing the role of chloroquine as an anti-HIV-1 agent are being planned in sub-Saharan Africa.⁴¹

Finally, blood safety needs to be addressed. Inadequate prevention and control of malaria leads to excess malaria-associated severe anaemia, which often requires blood transfusion.²¹ Although identified repeatedly as an important public health measure, blood safety remains poorly documented in many sub-Saharan African countries, and inadequate HIV-1 screening is likely to remain a widespread problem.⁴³

Public health implications

These recent studies show a clear interaction between malaria and HIV-1 in pregnant and non-pregnant adults in Africa. In east and southern Africa where HIV-1 prevalence approaches 30%, about a quarter to a third of clinical malaria in adults and malaria in pregnancy can be accounted for by HIV-1, leading to considerable public health implications.^{30,31,44} Thus, the worsening of malaria in Africa could be due in part to the expanding HIV-1 epidemic. Also, if present observations of a transient increase in viral load during malaria episodes, and its reversibility with effective treatment of malaria, hold in prospective studies, malaria control may be beneficial in curbing HIV-1 transmission and the rate of disease progression.

Perhaps the most critical challenge will be to make the most of increasing resources for control of malaria and HIV-1.⁴⁵ Anaemia-related deaths can be reduced by a joint programme of prevention of malaria-associated anaemia and provision of a safe blood supply.^{43,46} High rates of attendance at antenatal clinics in Africa suggest that the effects of HIV-1 and malaria in pregnancy could be countered in routine antenatal care by the incorporation of

malaria prevention, through intermittent preventive treatment and the use of insecticide-treated bed nets, and access to HIV-1 diagnosis and antiretroviral drugs. In conclusion, continued investigation into the interaction of HIV-1 and malaria, and joint programming of key intervention strategies could lead to immediate and long-term benefits in disease control.

STDs

Transmission of HIV-1 between adults in sub-Saharan Africa is mainly through heterosexual intercourse, and is enhanced in the presence of other STDs.¹⁰ Such diseases are highly prevalent in many parts of Africa, and could account for a substantial proportion of HIV-1 infections. Improved control of STDs has therefore been promoted as an effective strategy to reduce HIV-1 transmission, but its effect remains a subject of debate. HIV-1 infection, in turn, alters the clinical expression of some STDs, in particular genital herpes,^{47–49} which raises important issues for STD management guidelines.

Burden of STDs

Table 1 shows WHO estimates of the yearly incidence of curable STDs in sub-Saharan Africa.⁵⁰ The rate is the highest in the world, with 69 million new cases per year in a population of 269 million adults aged 15–49 years, although estimates are based on extrapolation of prevalence data from various sources and are considerably uncertain. However, STD rates are clearly high in many parts of Africa, and are one of the commonest reasons for adult attendance at outpatient clinics. Some of the most reliable data are derived from antenatal clinics in which women are screened and treated for syphilis. Reported rates of active syphilis range from 2.5% in Burkina Faso to 17.4% in Cameroon,^{51,52} several orders of magnitude higher than in western Europe.

High rates of STDs in Africa result from a combination of behavioural factors and poor health-service delivery. Risky sexual behaviour is affected by a mix of social, economic, and cultural factors, and its effects are compounded by poor access to preventive measures such as condom use. Restrictions in health-service delivery result in many STDs remaining infectious and uncured for long periods. Because HIV-1 and other STDs share the same mode of transmission, they tend to cluster in the same subpopulations, and surveillance data from STD clinics generally show much higher HIV-1 rates than in the general population. This clustering exacerbates the spread of HIV-1, especially in the early stages of an HIV-1 epidemic, since people with HIV-1 infection or who are exposed to HIV-1 are at increased risk of other STD infections.

Effects of STDs on HIV-1 transmission

STDs are thought to enhance HIV-1 transmission by increasing the infectiousness of HIV-1-positive individuals and the susceptibility of HIV-1-negative individuals by compromising mucosal integrity as a result of genital ulceration or inflammation, and by recruiting HIV-1 infected or susceptible target cells to the genital tract. Evidence for STD cofactor effects comes from observational studies showing strong associations between HIV-1 and STDs even after adjustment for confounding by risky sexual behaviour,^{11–13} and from biological studies of genital secretions from STD patients showing increased shedding of HIV-1 that decreases after treatment.^{53–55} The data suggest that ulcerative STDs, such as chancroid, syphilis, and herpes, have a stronger effect than non-ulcerative STDs, presumably because of greater disruption of the genital mucosa.

Panel 1: Overview of HIV-1 prevention trials in Mwanza, Rakai, and Masaka

	Mwanza	Rakai	Masaka
Baseline prevalence			
HIV-1	4% rising	16% stable	10% stable
<i>C trachomatis</i> *	5.5%	2.9%	1.5%
<i>N gonorrhoeae</i> *	2.8%	1.0%	1.4%
<i>T vaginalis</i> †	6.3%	29.5%	N/A
Active syphilis‡	6.3%	1.4%	0.7%
Intervention(s)	Improved syndromic treatment services	Mass treatment at 10-month intervals	A: Community-based behavioural intervention B: Behavioural intervention plus improved syndromic treatment
Trial design			
	Randomised by community 6 matched pairs Closed cohort (n~12 500) 24-month follow-up	Randomised by community 5 matched pairs Open cohort (n~14 000) 20-month follow-up	Randomised by community 6 matched triplets Open cohort (n~15 000) 36-month follow-up
Effect on HIV-1 incidence§	38% (95% CI 15 to 55)	3% (95% CI -16 to 19)	Awaiting publication
Effect on STD prevalence (final follow-up)	38% reduction in new cases of high-titre active syphilis 49% reduction in symptomatic urethritis (men) No significant reduction in NG/CT	20% reduction in active syphilis 41% reduction in TV (women) No significant reduction in NG/CT	Awaiting publication

TV=*T vaginalis*. NG=*N gonorrhoeae*. CT=*C trachomatis*. Data are from references 14, 62, 64, and A Kamali and K Orroth (personal communication). *Average prevalence of *C trachomatis* or *N gonorrhoeae* in people aged 15–39 years adjusted for diagnostic bias. †Prevalence of *T vaginalis* in women aged 15–49 years adjusted for diagnostic bias. ‡Average prevalence of high-titre active syphilis (*Treponema pallidum* haemagglutination+/rapid plasmin reagin test \geq 1.8) in people aged 15–54 years. §Calculated from relative risk in intervention compared with control groups, and adjusted for confounders and community randomised design.

Although the cofactor effects of STDs have been established, the sizes of such effects remain unclear. In longitudinal studies, relative risks of STDs range from 2 to 10, but are typically measured over long periods of follow-up and, since the STD is likely to have been present for only a small proportion of that time, the actual cofactor effect per sexual exposure might be several times higher than these values.⁵⁶ Conversely, estimated relative risks might have been overestimated because adequate control was not made for confounding by sexual behaviour.⁵⁷

Further evidence for the effects of STDs has come from an ecological study comparing two cities with very high HIV-1 prevalence (Kisumu, Kenya and Ndola, Zambia) and two with much lower prevalence (Cotonou, Benin and Yaoundé, Cameroon).^{58,59} Differences in HIV-1 prevalence between the cities could not be accounted for by variation in sexual behaviour, since Yaoundé had the highest rate of partner change. Differences in biological cofactors such as male circumcision and ulcerative STDs, which affect the per-contact probability of HIV-1 transmission, seemed more important than behaviour in driving the epidemics. Ulcerative STDs, especially herpes,⁶⁰ were much more frequent in the high prevalence cities. One of the most striking findings was the high prevalence of HIV-1 infection—more than 20% by age 20 years—in young women in Kisumu, who reported only one or two sexual partners.⁶¹ Even with allowance for some under-reporting of risk behaviour, to account for such a high incidence of infection is difficult without assuming the presence of biological cofactors that increase the probability of transmission.

STD control for HIV-1 prevention

HIV-1 control measures include improved STD management, which aims to reduce the prevalence of STDs and hence the probability of HIV-1 transmission. Although the rationale for this indirect approach to HIV-1 prevention is clear, its probable effect is difficult to predict. The effect depends on the prevalence of treatable STDs in partners who are HIV-1 discordant (one partner positive, the other negative); the frequency of sexual contact between partners;

the magnitude of the STD cofactor effect on HIV-1 transmission; and the effectiveness of any specific STD control programme in reducing STD prevalence. None of these factors is easy to estimate, which has led to trials in east Africa designed to obtain direct measures of the effect of control measures for STDs in specific populations.

Three trials have been completed; panel 1 summarises the key findings. The first, in Mwanza, Tanzania, showed that improved STD treatment services, delivered through local health units, reduced HIV-1 incidence in the general population by around 40%.¹⁴ Incidence of new cases of active syphilis also fell sharply.⁶² Because diagnostic facilities were unavailable in most health units, as in much of Africa, the programme relied on syndromic treatment, whereby treatment was provided for the main causative agents for signs such as genital ulcers or discharge.

The Mwanza intervention depended on patients recognising symptoms and presenting for treatment; the effectiveness of this approach might be compromised since many STDs are asymptomatic and not all people with symptoms present to health units for treatment.^{63,64} In an attempt to overcome these limitations, in the second trial in Rakai, Uganda, the effect of mass treatment of the population for common bacterial STDs was measured on rates of HIV-1 infection. Disappointingly, although reductions were seen in some STDs, there was no significant effect on HIV-1 incidence.⁶⁵

A third trial was done in Masaka, Uganda, to assess the effect of a community-based behavioural intervention with or without the provision of improved STD treatment services, by use of the syndromic approach. Despite reductions in STDs and changes in reported behaviour, neither the behavioural nor the STD treatment intervention had a significant effect on HIV-1 incidence (A Kamali, personal communication).

The contrasting findings have led to much confusion, but could be because of differences between interventions (continuous provision of syndromic services *vs* intermittent mass treatment), or differences between populations.^{10,66,67} The findings from Masaka lend support to the view that differences between populations provide the main

explanation for the different results in Tanzania and Uganda. Detailed reanalysis of trial data has shown there are two crucial population differences. First, at the time of the trials, there was much less risky sexual behaviour in Uganda than in Tanzania, resulting in much lower rates of curable STDs (panel 1). Risk behaviour and STDs probably rose steeply in Uganda during civil disruption in the 1970s and 1980s, leading to the explosive epidemic of HIV-1 infection, and have since fallen after intensive health education programmes. Second, the HIV-1 epidemic in Uganda is at an advanced stage and is no longer concentrated in high-risk groups. As a consequence, much new infection now occurs between stable partners in whom the risk of HIV-1 transmission is high even without STD cofactors, because of repeated exposure.⁶⁸ Thus, the proportion of new HIV-1 infections attributable to STDs is much higher in Tanzania than Uganda.^{69,70}

These findings have important implications for control programmes. First, they show the importance of intervening early to achieve the most from STD control measures. Second, STD rates in sub-Saharan Africa are very variable; the fairly low rates in Uganda might not be typical of other parts of Africa with severe HIV-1 epidemics. For example, STD rates in South Africa are extremely high.^{50,71} Wherever STDs are highly prevalent, institution of improved management of STDs is an essential component of HIV-1 control.

Genital herpes

In Africa, HIV-1 and herpes simplex virus type-2 (HSV2) have a synergistic relation. HSV2 infection is widespread, with seroprevalence rising to 70–80% by age 30 years in some parts of eastern and southern Africa.^{60,72,73} Rates seem to be somewhat lower in west Africa, where HIV-1 spread is also less extensive.⁶⁰ The reasons for geographical variation in HSV2 prevalence are unclear, although male circumcision may be protective against HSV2 as well as HIV-1 infection, which might provide part of the explanation.⁷⁴

As in other ulcerative STDs, strong evidence shows that HIV-1 transmission is enhanced by HSV2 infection. In a meta-analysis of data from longitudinal studies, HIV-1 risk was doubled in HSV2-seropositive individuals;⁷⁵ even stronger associations have been noted.^{76,77} However, whether the effect of HSV2 is concentrated during clinical episodes of herpes, or whether HIV-1 transmission is also enhanced during the subclinical phase of HSV2 infection is unclear.

Because of the high prevalence of HSV2 infection in many parts of Africa, the disease might account for a substantial proportion of HIV-1 infections. Since genital herpes is an incurable lifelong infection that is not effectively controlled by existing measures, an important issue is whether there are new interventions that could reduce the cofactor effect of herpes.⁷⁸ There are significant delays in seeking STD treatment in most parts of Africa; thus, patients are likely to shed HSV2 for some time before treatment. Episodic treatment with antiviral drugs would therefore have little effect on HIV-1 transmission unless enhanced by parallel health education targeting early symptom recognition and prompt treatment. A more intensive strategy would be to prevent recurrent episodes by continuous suppressive drugs, but the potential for widespread provision is limited by issues of compliance, cost, and feasibility—although it might be possible to target such treatment to high-risk groups in populations in which they have an important role in spreading HIV-1 infection. Effective HSV2 vaccines that prevented infection or reduced clinical expression in infected

Panel 2: STD and HIV-1 prevention research priorities

Research topic

- Trials of combined interventions (mass treatment plus syndromic treatment services) especially in populations with a high prevalence of curable STDs
- Trials of interventions targeted at high-risk groups. For example:
 - Periodic presumptive treatment of sex workers
- Trials of interventions to protect adolescents and young people against HIV-1 and other STDs
- Operational research to assess strategies to increase coverage of effective STD treatment. For example:
 - Through involvement of private/informal health providers and promotion of appropriate treatment-seeking behaviour
- Improvement of treatment algorithms for vaginal discharge, through development and validation of point-of-care tests for gonorrhoea and chlamydia
- Monitoring of drug sensitivity, especially for gonorrhoea, to validate treatment algorithms in different populations
- Operational research to determine whether specific therapy for herpes should be added to the treatment algorithms for genital ulcers
- Trials of the effects of episodic or suppressive herpes treatment on HIV-1 transmission
- Development and assessment of HSV2 vaccines, including their effect on HIV-1 transmission
- Assessment of the effects of candidate vaginal microbicides on the incidence of STDs

individuals would be the most attractive option for control, and the potential for a substantial effect on HIV-1 transmission presents a strong case for prioritisation of further development and testing of such vaccines.

The interaction between HIV-1 and HSV2 works in both directions, since the clinical course of HSV2 infection is exacerbated by HIV-1 infection, with more frequent, more severe, and longer clinical episodes.^{47,48} This bidirectional relation can give rise to positive feedback, with HSV2 enhancing HIV-1 transmission, which in turn leads to increased HSV2 transmission. A further consequence is raised prevalence of herpes in STD patients with genital ulcers. An important issue for clinical services is whether treatment algorithms for genital ulcers should be adjusted, at least for severe herpetic lesions that are likely to be HIV-1-related.⁷⁸

Implications

High STD prevalence in Africa is almost certainly one of the factors driving the explosive spread of HIV-1 infection. Although behaviour change or effective service provision has reduced STD rates in some countries, in general, treatment is inadequate and STD rates unacceptably high. Thus, alongside promotion of safer sexual behaviour and condom use, improved STD treatment remains an important component of HIV control programmes. Effects of such interventions will be greater in countries with high STD rates and in subpopulations at high risk of STDs. The effects of STD control might decline as HIV-1 epidemics mature and the virus spreads beyond core groups with high rates of change of sexual partners. More effective interventions against STDs, especially genital herpes, are urgently needed (panel 2).

Tuberculosis

The HIV-1 epidemic has greatly worsened tuberculosis control in Africa.^{16,17} Figure 2 shows national tuberculosis

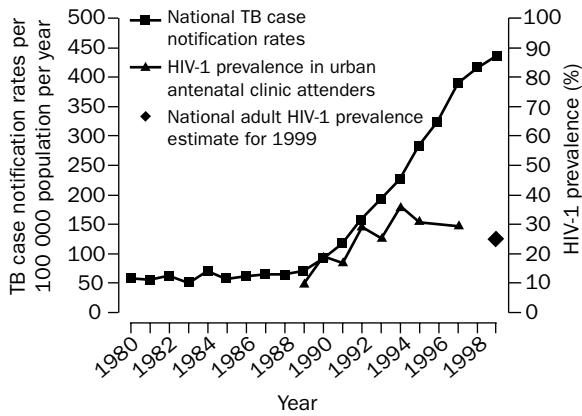


Figure 2: National tuberculosis case notification rates in Zimbabwe and antenatal HIV-1 prevalence in Harare and Bulawayo⁷⁹

TB=tuberculosis.

case notification rates and estimates of HIV-1 prevalence for pregnant women attending antenatal clinics in the two major cities in Zimbabwe, where HIV-1 prevalence has been high for more than a decade.⁷⁹ Table 2 shows WHO estimates of the burden of tuberculosis infection, disease, and HIV-1 co-infection rates in sub-Saharan Africa; Botswana, which had the highest worldwide adult HIV-1 prevalence in 1999; and the USA, which has one of the lowest national incidences of tuberculosis.¹⁷ Tuberculosis is projected to continue rising by about 10% per year in the African countries most severely affected by HIV-1.^{17,79} It is one of the most frequent serious HIV-1 associated infections, and the commonest cause of death in HIV-1 positive Africans.⁷ Mortality during treatment of HIV-1-associated tuberculosis is high, especially when cheaper treatment regimens are used.⁸⁰ The only relief in an otherwise grim picture is that in most African countries,^{81,82} drug-resistant tuberculosis is no more associated with HIV-1 than fully sensitive tuberculosis, and sensitivity to first-line tuberculosis drugs remains high.⁸¹⁻⁸³

	Sub-Saharan Africa	Botswana	USA	UK
Whole population				
Population size (millions)	640	1.5	283	59
TB incidence (per 100 000 population per year)	313	762	5	12
Yearly increase in TB incidence	3-4%	9.0%	-7.7%	0.1%
Prevalence of latent TB infection	35%	42%	7%	13%
15-49 year olds				
HIV-1 prevalence	8.7%	36%	0.6%	0.1%
HIV-1/TB co-infection	3.4%	17%	0.04%	0.01%
HIV-1 prevalence in TB patients	37%	77%	27%*	6%*
Fraction of TB cases attributable to HIV-1 infection	30%	64%	26%*	6%*
Estimated yearly number of TB cases attributable to HIV-1 infection	440 000	5400	2300	240

TB=tuberculosis. *Prevalence of HIV-1 in TB patients compared with that of the general population is high in the USA and UK, therefore attributable fractions are also fairly high. This probably relates to non-random distribution of TB and HIV-1 infection within more affluent populations, in which specific minority groups are at disproportionately high risk of being infected with both TB and HIV-1.

Table 2: Estimated burden of HIV-1-associated tuberculosis in sub-Saharan Africa, Botswana, USA, and UK¹⁷

Panel 3: Major factors contributing to the HIV-1-associated tuberculosis epidemic in Africa

Contributing factor

- High reactivation rate of latent TB infection if also infected with HIV-1⁸⁴
Plus latent TB infection widespread in Africa^{17,86}
- High risk of rapidly progressive disease if infected with TB once HIV-1+ve⁸⁵
Plus exposure to ongoing TB transmission^{17,86}
- Difficulties in obtaining lasting cure with currently available treatment regimens due to long length and need for good adherence⁸⁶
High risk of chronic infectious TB instead of cure if adherence poor
Exacerbated by acquired or initial drug resistance
High recurrence rates if adherence poor
- High TB transmission rates in the community^{86,93,94}
High TB incidence plus diagnostic delays
High burden of HIV-1-associated TB may feedback to increase transmission further⁹⁴
- High nosocomial TB transmission rates
High risk of exposure to nosocomial TB infection once symptomatic with HIV-1
Increasing % of admissions to hospital due to TB since the start of the HIV-1 epidemic⁷

TB=tuberculosis.

Latent and recently acquired tuberculosis infection

Panel 3 shows the main factors contributing to the magnitude of the HIV-1-associated epidemic of tuberculosis. HIV-1 infection increases the risk of both reactivation of latent tuberculosis infection⁸⁴ and the risk of rapidly progressive disease soon after infection or reinfection with tuberculosis.^{16,85} Latent tuberculosis infection was already highly prevalent in Africa before the spread of HIV-1, and in consequence at least a third of HIV-1-infected Africans are co-infected with tuberculosis.¹⁷ People co-infected with HIV-1 and tuberculosis develop tuberculosis disease at high rates of between 3000 and 10 000 per 100 000 person-years unless their latent tuberculosis infection is treated.⁸⁴ Treatment of latent tuberculosis infection in HIV-1-infected people is cheap, effective, and internationally recommended, but logistical difficulties and poor health infrastructures have so far restricted the scale of implementation in Africa. Prevention of reactivation of tuberculosis in this large pool of co-infected individuals is, however, one of the key challenges that must be met if tuberculosis control in Africa is to improve.

The second major challenge is continuing tuberculosis transmission. Recently acquired tuberculosis infection poses an appreciable risk to healthy adults, even those who are HIV-1-negative and have been previously infected with tuberculosis.⁸⁶⁻⁸⁸ 10-20% of HIV-1-negative adults infected with tuberculosis are estimated to develop disease at some time during their life, with about half the risk in the first 2 years.^{86,88} Because of this high early risk, asymptomatic household contacts are offered preventive therapy in many affluent countries.

Effect of HIV-1 on tuberculosis transmission rates

Data for tuberculosis transmission rates in endemic settings are sparse, and the effect of HIV-1 is thus still unclear. Panel 4 shows data from studies of household contacts,⁸⁹ tuberculosis strain typing,^{82,90-92} and age-trends in tuberculin skin test reactivity in children.^{86,93,94} Results of tuberculosis strain typing studies suggest that about half of tuberculosis

Panel 4: Tuberculosis transmission in Africa and the effect of HIV-1

Study type	Findings
Household contact studies	
<ul style="list-style-type: none"> ● Examine household contacts of HIV-1+ve and HIV-1-ve TB patients for TB infection (skin test reactivity), or disease, or both 	<ul style="list-style-type: none"> ● HIV-1+ve TB no more infectious than HIV-1-ve TB and may be less so*⁸⁹ ● HIV-1 prevalence higher in households of HIV-1+ve TB than HIV-1-ve TB patients¹⁰⁶ ● Additional cases of active TB more common in contacts of HIV-1+ve than HIV-1-ve TB patients¹⁶
Population-based TB fingerprinting (RFLP) studies	
<ul style="list-style-type: none"> ● Examine links between clusters of patients who share TB strains with the same RFLP pattern, and risk factors for having a clustered isolate 	<ul style="list-style-type: none"> ● 40–50% of African TB patients have clustered isolates^{82,90–92} Clustering suggests TB from recently acquired transmission rather than reactivation ● Having a clustered isolate is independent of HIV-1 status^{82,90–92} † Suggests that HIV-1 increases risk of reactivational and early progressive TB by a similar factor ● Known links for only about a quarter of patients in same cluster:^{82,90–92} often to congregate settings—eg, bars, hospital, prisons Suggests high % of transmission events are to casual contacts ● Increased risk of recurrence after HIV-1+ve TB is due to greater susceptibility to disease following reinfection⁸⁵
Tuberculin surveys in children	
<ul style="list-style-type: none"> ● Age-trend in tuberculin reactivity can be used to estimate infection rate as annual risk of tuberculous infection (ARTI) 	<ul style="list-style-type: none"> ● 1970/80s: slow exponential decline in ARTI from a risk of about 2–5% per year to about 0.5–1% per year⁸⁶ ● After HIV-1: Tanzania: ARTI stable at 0.6% per year⁹³ Kenya 1986/96: ARTI up from 0.6% to 1.1% per year, and from 0.9% to 2.9% per year in Nairobi⁹⁴

TB=tuberculosis. RFLP=restrictive fragment length polymorphism. *Consistently significant in US studies, but a less consistent feature of African HIV-1-infected TB patients, who are more often smear positive and have a higher median CD4 count at diagnosis than their US counterparts. †By contrast, clustering is HIV-1-associated in the USA, indicating that in some settings HIV-1 may be a stronger risk factor for recently transmitted TB than for reactivational TB.

cases in endemic settings are attributable to recent transmission in all patients, irrespective of HIV-1 status.^{82,90–92} Hence, transmission is an important determinant of tuberculosis incidence, and any rises in tuberculosis transmission will quickly feed back in a cycle of increasing disease and transmission. Data from household contact studies suggest that HIV-1-associated tuberculosis is less infectious per case than HIV-1-negative tuberculosis, although this difference is less striking and consistent in African than in American patients.⁸⁹ The effect of HIV-1-associated tuberculosis on transmission rates might, therefore, be offset by fewer secondary infections generated by each case. This factor might partly account for the stable yearly risk of tuberculosis infection in Tanzanian children during a 15-year period in which the incidence of tuberculosis rose four-fold.⁹³ In Kenya, however, tuberculosis transmission rates increased during the 1990s, mainly in districts with a high HIV-1 prevalence, such as Nairobi.⁹⁴

Communal settings, including mines, hospitals, prisons, and bars are important sites of tuberculosis transmission.^{82,91,92} In particular, health-care facilities in Africa are being overwhelmed by the rising burden of HIV-1-infected patients, in whom active tuberculosis is one of the most common causes for admission.^{6,7} In a Kenyan teaching hospital, 47% of patients dying in a medical ward had active tuberculosis; only half the cases were suspected before death, showing the extent to which HIV-1-associated tuberculosis can be underestimated.⁶ Although recommendations to keep nosocomial tuberculosis transmission to a minimum in resource-poor settings exist, some degree of exposure is inevitable while tuberculosis incidence remains high and diagnosis imprecise.

Tuberculosis control in settings with high HIV-1 prevalence

International recognition of the global threat posed by the HIV-1 and tuberculosis epidemics has come most recently from the establishment of the United Nations Global Fund

to Fight AIDS, tuberculosis, and Malaria.⁴⁵ Panel 5 shows the complementary strategies, DOTS⁷⁹ (directly observed treatment, short course) and ProTEST (promoting testing for HIV-1 and TB),¹⁶ that are being promoted by WHO and UNAIDS (Joint United Nations Programme on HIV/AIDS). The DOTS strategy includes standardised diagnosis, treatment, and monitoring with the aim of reducing diagnostic delays for smear positive (infectious) tuberculosis patients, keeping the risk of inducing or adding to drug resistance to a minimum, and increasing the likelihood of a successful treatment outcome. The emphasis is on outcome because a common failing of tuberculosis treatment programmes is a high default or interruption rate.^{79,86} Low rates of treatment completion are associated with generation of drug resistance⁸⁶ and stabilisation of pulmonary tuberculosis in a chronic form with minimum progression that can remain infectious for many years unless treated again.⁸⁶

Although DOTS forms the cornerstone of tuberculosis treatment programmes, it has no element aimed at direct prevention of tuberculosis in high-risk individuals, and is not sufficient to contain tuberculosis incidence in the face of rising HIV-1 prevalence.^{95,96} ProTEST is intended to help fill this gap by promoting early HIV-1 diagnosis through voluntary counselling and HIV-1-testing (VCT), followed by screening and treatment of latent tuberculosis co-infection in HIV-1-positive individuals.⁹⁷ Voluntary counselling and HIV-1-testing linked to continuing care is a key element of HIV-1 prevention in high-prevalence settings, but only very broad implementation would have an appreciable effect on community tuberculosis incidence.⁹⁷ Results from feasibility studies have generally shown disappointing low rates of delivery, with considerable drop-out at each step in the screening and treatment process.⁹⁷ Hopefully, antiretroviral drugs will soon be added to the package of care offered to HIV-1-positive individuals. Such treatment might not only stimulate demand for voluntary counselling and HIV-1-testing, but also contribute to

Panel 5: **Established tuberculosis control strategies**

Strategy	Target population and components	Strengths and weaknesses
BCG vaccination	Neonates in high TB burden countries	<ul style="list-style-type: none"> ● Personal protection from disseminated TB <i>But</i> <ul style="list-style-type: none"> ● ? No protection from TB infection or pulmonary TB ● No effect on TB transmission
DOTS⁷⁹ (Directly observed therapy, short course) <ul style="list-style-type: none"> ● WHO TB control strategy aimed at National level 	Symptomatic TB patients <ul style="list-style-type: none"> ● Diagnosis based on sputum smears ● Standardised treatment regimens ● Minimise default/interruption by DOT and ensuring drug supply ● Monitor and report treatment outcomes 	<ul style="list-style-type: none"> ● Highly cost effective ● Widely implemented ● Can lead to reduced transmission rates by efficient diagnosis and treatment of smear +ve TB ● Maintains drug sensitivity <i>But</i> In high HIV-1 settings: <ul style="list-style-type: none"> ● Nothing to prevent reactivational HIV-1/TB ● Insufficient to stop increase in TB incidence
ProTEST¹⁶ <ul style="list-style-type: none"> ● New WHO strategy being piloted in high HIV-1 prevalence countries 	HIV-1/TB co-infected individuals <ul style="list-style-type: none"> ● Provide HIV-1 diagnosis through VCT ● Screen for TB disease ● Treat latent TB infection in HIV-1+ves 	<ul style="list-style-type: none"> ● Strengthens HIV prevention programme <i>But</i> Will only improve TB control if: <ul style="list-style-type: none"> ● Widely implemented ● Achieves high VCT uptake and good adherence to TB preventive therapy
Household contact tracing⁸⁹ <ul style="list-style-type: none"> ● Recommended for low, but not high, TB burden countries 	Individuals at high risk of TB due to recent exposure: <ul style="list-style-type: none"> ● Trace contacts of smear +ve TB ● Screen for and treat TB disease/infection 	<ul style="list-style-type: none"> ● Identifiable high risk group <i>But</i> <ul style="list-style-type: none"> ● Consumes extra resources ● Efficacy undermined by high TB transmission ● Most transmission is to community, not household
Active case finding <ul style="list-style-type: none"> ● Systematic mass screening for active TB^{86,96} 	High risk populations—eg, immigrants and miners <ul style="list-style-type: none"> ● Radiograph either with or without symptom screen ● Sputum testing if symptoms or radiograph abnormal 	<ul style="list-style-type: none"> ● High pick-up rates in endemic settings ● Reduces transmission by diagnosing chronic TB cases ● Provides estimate of TB disease prevalence <i>But</i> <ul style="list-style-type: none"> ● Expensive ● Needs to be repeated periodically
Mass prevention therapy campaigns¹⁰²	Epidemic situations <ul style="list-style-type: none"> ● Mass screening ● Treatment for either active TB or presumed latent TB 	<ul style="list-style-type: none"> ● Reduces TB incidence and transmission ● Reduces prevalence of latent TB <i>But</i> <ul style="list-style-type: none"> ● Expensive ● Need continuing intensified control to maintain benefits

TB=tuberculosis. ProTEST=promoting testing for HIV-1 and TB. VCT=voluntary counselling and HIV-1 testing. ?=uncertainty.

reduced mortality and tuberculosis prevention by restoring and preserving immune function.⁹⁸⁻¹⁰⁰

Other options for improving tuberculosis control do exist (panel 5), although none is being considered for widescale adoption in Africa. Household contact tracing is widely practised in countries with low tuberculosis incidence, with the focus on treating recently acquired tuberculosis infection.^{86,89} Before the HIV-1 epidemic, this approach was judged impractical in high-burden settings while tuberculosis transmission rates remained high, especially since the pick-up rate of active tuberculosis disease in contacts was low except in young children.⁸⁶ However, this argument needs to be reassessed and reconsidered in view of active promotion of tuberculosis preventive therapy. As

with ProTEST, however, there are limitations of scale, in this instance because most tuberculosis transmission does not take place within households.^{86,91,92,101}

Two strategies that are not restricted by scale are active case-finding and mass preventive treatment campaigns. Active case-finding through direct questioning, radiography, or both is still practised to reduce the prevalence of active tuberculosis in certain high-risk populations.⁹⁶ The strategy is effective, but costly and logistically demanding. Mass preventive treatment was used to control epidemic tuberculosis successfully in Alaska in the 1960s, and is the only strategy that can rapidly and simultaneously reduce tuberculosis transmission, incidence, and latency rates.¹⁰²

Panel 6: Research that could lead to improved tuberculosis control

Research output

- HIV-1 vaccine
Ideally capable of slowing progression of HIV-1, as well as protecting against HIV-1 infection
- More effective TB vaccine
Ideally capable of preventing reactivational TB as well as protecting against rapidly progressive pulmonary TB
- Drugs effective against latent/dormant TB bacilli¹⁰³
Potential for ultrashort regimens to treat TB disease and latent infection
- Rapid diagnosis of latent TB infection^{104,105}
Ideally requiring very little infrastructure—eg, whole blood dipstick
- Diagnostic test capable of distinguishing recent from remote TB infection
Would allow direct measurement of TB transmission rates to adults, which is not presently possible in endemic settings
Would enable trends in transmission rates to be monitored in communities and health-care settings
- Rapid diagnosis of TB disease
Improve diagnostic accuracy for smear -ve disease
If very rapid and very cheap—eg, breath-based—then would facilitate mass screening and active case-finding¹⁰⁷

TB=tuberculosis.

Although a massive undertaking, an intervention including preventive drugs on a national scale might be the only effective approach for a country such as Botswana, where an estimated 17% of adults were co-infected with HIV-1 and tuberculosis at the start of the millennium.¹⁷ However, because *M tuberculosis* is able to enter latency, the shortest effective regimen to prevent tuberculosis lasts for 2 months and the cheapest for 6–9 months.⁸⁴ Latency is a temporary but prolonged metabolically quiescent state during which the bacterium cannot be killed by standard chemotherapy. The molecular basis of latency is being elucidated, and a class of compounds that can kill even metabolically inactive mycobacteria has been identified, raising the prospect of combining ultra-short standard chemotherapy with drugs able to activate or kill latent mycobacteria.¹⁰³

Prospects

Effective ultra-short regimens to treat tuberculosis infection and disease would transform tuberculosis prevention and management. Panel 6 shows other advances that could improve prospects for tuberculosis control. Development of reliable HIV-1 test kits that give results within 1 h, at low cost, and without the need for laboratory facilities, has greatly expanded the scope for targeting large-scale interventions to rural and urban HIV-1-infected Africans.⁹⁷ Equivalent tests for recent or latent tuberculosis infection and active tuberculosis have so far remained elusive. Immunodominant T-lymphocyte responses have been identified and used in diagnosis, but tests based on cellular immune responses are intrinsically more elaborate than antibody-based tests and are not yet simple enough to allow cheap and rapid diagnosis outside laboratories.^{104,105} Indeed, the tuberculin skin test remains the most accessible test for tuberculosis infection, and sputum smears still form the basis of rapid tuberculosis diagnosis in resource-poor settings.

Although a well coordinated international response could reduce the burden of HIV-1-associated tuberculosis, even with the imperfect methods available, this approach would require commitment and funding on a hitherto unseen level.⁴⁵ Without substantial assistance from the rest of the world, rising tuberculosis incidence and mortality rates will continue to take an increasing toll in the African nations severely affected by HIV-1.

Conclusions

The HIV-1 epidemic in Africa has reached such an extreme magnitude that further major consequences are inevitable, and will include increasing difficulty in controlling other infectious diseases. One of the cruel ironies is that the severity of the African HIV-1 epidemic is in itself a direct reflection of the impoverished and imperfect nature of health care that preceded the epidemic, notably poor control of STDs. Improvements were made in infectious disease control in Africa during the last half of the 20th century, but to a limited extent that left endemic disease and transmission rates well above those of more-developed countries. HIV-1 has now so compounded this situation that it would take a massive scale of interventions to return regional health to pre-epidemic standards. Without intervention, however, public health will become more difficult and expensive to maintain as the incidence, transmission, and drug resistance of other endemic diseases are affected by HIV-1.

Our ability to define and monitor the full effect of the HIV epidemic is seriously compromised by scarce research and routine surveillance data for most infectious diseases in Africa. There remain important unanswered questions: are the incidences of tuberculosis, malaria, STDs, and other infectious diseases increasing in HIV-1-negative Africans because of HIV-1? Are helminth diseases such as schistosomiasis and filariasis affected by HIV-1? To what extent, if at all, is HIV-1 progression affected by frequent concurrent infections? Surveillance of disease trends and research into infectious disease control should be priorities in countries severely affected by HIV-1, and public health investment and standards should be enhanced to cope with the new realities of infectious disease control since the HIV-1 epidemic.

Contributors

The sections on malaria, STDs, and tuberculosis were written by R Steketee and F ter Kuile, A Kamali and R Hayes, and E Corbett and A Latif, respectively. E Corbett wrote the introduction and conclusions, and all authors contributed to review and revision of the final manuscript.

Conflict of interest statement

None declared.

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