HIV prevention before HAART in sub-Saharan Africa

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Data on the cost-effectiveness of HIV prevention in sub-Saharan Africa and on highly active antiretroviral therapy (HAART) indicate that prevention is at least 28 times more cost effective than HAART. We aim to show that funding HAART at the expense of prevention means greater loss of life. To maximise health benefits, the next major increments of HIV funding in sub-Saharan Africa should be devoted mainly to prevention and to some non-HAART treatment and care. Funds should be allocated to HAART primarily for demonstration projects that will help prepare for scaled-up HAART provision following broad population coverage by prevention programmes. UNAIDS and the London School of Hygiene and Tropical Medicine recently estimated that at least US$9·2 billion annually is required to mount an appropriate response to the HIV pandemic, including substantial funding for HAART. To date, US$1·96 billion has been committed to the newly-established UN Global Fund to Fight AIDS, Tuberculosis, and Malaria. It is a moral imperative that expanded programmes to control HIV be implemented without delay, and that the goal of US$9·2 billion or more in annual spending be attained as rapidly as possible. The findings and recommendations of this analysis pertain to the phasing in of additional HIV-related activities during the current period of improved but inadequate funding.

A major policy debate is underway on the best allocation of new money for the control of HIV in sub-Saharan Africa. Proponents of increased spending for HIV prevention clash with those who believe that new allocations should be dedicated to treatment of infected individuals with highly active antiretroviral therapy (HAART). Few health-policy questions carry higher stakes. The lives of millions depend on getting the answer right.

Many groups lament the schism between the two camps and seek to avoid direct competition for funding between HAART and prevention.[1] A debate about the prevention-HAART trade-off is both inevitable and needed when the availability of finance for responding to AIDS is acutely insufficient and limiting. We show that cost-effectiveness data indicate that targeting prevention should be a primary focus of HIV spending in sub-Saharan Africa.

At industrialised world prices of $10 000–12 000 per patient-year, the costs of a major programme of HAART distribution in sub-Saharan Africa were so untenable as to receive no serious consideration. Until recently, therefore, most of the discussion about HAART in sub-Saharan Africa centered on the best methods to persuade pharmaceutical companies to establish special low prices for antiretroviral drugs in less-developed countries. The terms of the debate changed in two ways during the past year.

First, treatment activists persuaded pharmaceutical companies to reduce drug prices in poor countries. Concessions have been most dramatic for antiretroviral drugs used in mother-to-child transmission prevention programmes but have also included antiretroviral

treatment for adults. More recently, sporadic price reductions were superseded by a radical break from previous pricing. This transformation occurred in February, 2001, when the Indian pharmaceutical company Cipla offered HAART for US$350 per person-year for distribution by Médecins Sans Frontières if they agreed to take responsibility for distribution in a given setting. Treatments which were previously unaffordable suddenly seem within reach.

Second, more money is now at stake. The international HIV conference held in Durban, South Africa in July, 2000, did much to increase awareness in the industrialised world about the seriousness of the HIV pandemic in sub-Saharan Africa. Discussions of increased funding for HIV control ensued, intensifying in preparation for the UN General Assembly Special Session on HIV/AIDS held in June, 2001. The UN's Global Fund to Fight AIDS, Tuberculosis, and Malaria, which was established in anticipation of this meeting, has received pledges totalling US$1·96 billion of new funding as of March 16, 2002.[2] A substantial portion will be spent in sub-Saharan Africa to combat AIDS. How this money is spent is of key concern.

The global AIDS pandemic is on a trajectory to be among the most devastating events in human history. 37 million people are currently infected with HIV, 25 million of these in sub-Saharan Africa.[3] HIV was the leading cause of death in Africa in 1999 and accounted for twice (20·6%) as many total deaths as its nearest competitor, acute lower respiratory infection (10·3%).[4] In Botswana, 40% of adults are infected. In much larger South Africa, 20% of adults and an astonishing 65% of military personnel are infected.[5] Life expectancy in the worst AIDS-afflicted countries has dropped by 20 years, erasing decades of gains. HIV has moved beyond the province of public health alone and has become a social, economic, and security concern.

An effective prevention and treatment response

Two recent studies estimated the cost of an effective response.[6,7] One concluded that $9·2 billion would be needed annually.[6] This estimate is roughly consistent with an earlier estimate of at least $7·5 billion annually.[7] The

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higher figure of $9·2 billion represents 0·044% of the combined gross national product of the 22 wealthy donor countries constituting the Development Assistance Committee of the Organization for Economic Cooperation and Development (OECD).[7] As indicated by their contributions to the new UN Global Fund to Fight AIDS, Tuberculosis, and Malaria, AIDS-afflicted countries will contribute substantial sums to an enhanced HIV prevention effort. The UNAIDS study estimated that one-third to half of the total could come from domestic resources, thus reducing the cost to the wealthy nations to an extremely modest 0·022% of combined gross national product. Clearly, a scaled-up response including both prevention and substantial commitments to HAART is affordable.

Estimates of current global spending for HIV vary considerably, depending upon the methods used. However, all estimates indicate that the current commitment to HIV prevention and treatment is incommensurate with the magnitude of the pandemic. In 2000, the combined annual contribution of international aid donations for HIV prevention and treatment from the OECD nations was approximately $140 million, well below 3% of the amount needed to stem the pandemic.[7] A more inclusive approach that accounted for all HIV expenditures in low and middle-income countries concluded that about $1·8 billion was spent in 2000. Of this sum, $1 billion was spent for care and support and $0·8 billion for prevention.[8] This sum constitutes only 20% of the $9·2 billion recommended total. We are far from achieving the level of funding needed.

How could money be best spent in the interim?

While the world debates how to achieve the full $9·2 billion needed, we need to decide how the next incremental contributions shall be spent.

A dominant theme heard from many policy makers and analysts is that treatment and prevention must go hand-in-hand. This rhetoric often fails to distinguish between treatment of opportunistic infections and palliative care, which is inexpensive and often highly cost effective,[9] and HAART, which is both more costly and more effective. Combining the two under the rubric of treatment may provide some temporary political cover but is ultimately confusing. This article focuses specifically on HAART. We refer to a triple-drug regimen typically consisting of two

nucleoside analogues and a protease inhibitor or a non-nucleoside agent such as nevirapine.

If the goal is to minimise total loss of life, we believe new increments of spending for HIV in sub-Saharan Africa should be allocated for prevention and some treatment of opportunistic infections and palliative care. Funds should be allocated for HAART, only where doing so demonstrably leverages net increases in prevention funding or helps plan HAART programmes in anticipation of a time when more resources are available. This is because prevention is far more cost effective than HAART. This means allocation of limited funds to prevention rather than to HAART can save far more lives.

Two recent reviews of the cost-effectiveness of ten prevention options in the less-developed world found that they ranged from actually saving the health system money to costing US$18 per disability adjusted life years (DALYs) saved.[10,11] Most estimates cluster in the range of US$5–18 per DALY (table 1).

We assumed an average of US$12·50 per DALY for additional spending on HIV prevention. Prevention funds could be distributed across a variety of effective programme activities to obtain this result (table 2). The actual figure can be expected to vary by local circumstances, programme scale, and the mix of interventions selected.

To bias our estimate in favour of HAART, we make a set of assumptions that serve to generate an unrealistically favourable estimate of the cost-effectiveness of HAART:

- Those receiving HAART enjoy the same quality of life as the HIV-uninfected (ie, no drug side-effects or opportunistic infections).
- No costs accrue to distribute, store, and dispense the drugs.
- Patients receiving HAART require no monitoring, testing, and counselling.
- The availability of HAART does not increase the risky behaviour of patients or of the HIV-uninfected individuals in the surrounding population.
- No drug-resistant strains of HIV develop because of imperfect adherence to HAART.

The cost-effectiveness of HAART is compared with no intervention rather than with non-antiretroviral treatment options. In an incremental cost-effectiveness analysis, HAART would look far less favourable. For example,

Intervention population	Intervention	Cost per DALY (US$)	Cost per case averted (US$)	Study country	Ratio of CE of this intervention to CE of HAART[*]	Reference
Sex workers	STD control and condom promotion	<1	8–12	Kenya	<350	12
General	STD control	13	350	Tanzania	27	13
General	Voluntary counselling and testing	Overall: 12·77 17·78 HIV+ male as couple: 2·75 4·48 HIV+ female as couple: 3·38 2·96	Overall: 249 346 HIV+ male as couple: 54 87 HIV+ female as couple: 68 58	Kenya, Tanzania	27 20 127 78 104 118	14
High-risk women	Female condom promotion	Savings to health payer	Savings to health payer	South Africa	100+	15
General	Safe blood supply	8	172	Uganda	44	16
General	Mother-to-child transmission			Uganda		17
30%, HIV prevalence		11	298		18	
15%, HIV prevalence		19	506		32	

STD=sexually transmitted disease. Cost-effectiveness (CE) of HAART assumed to be $395 per DALY (favourable assumptions).

Table 1: **Cost-effectiveness of HIV prevention interventions in sub-Saharan Africa**

	Cost per DALY (US$)	Budget allocation
MTCT prevention	19·00	20%
Female condoms for sex workers	1·00	10%
STD control for sex workers	1·00	10%
STD control (general)	13·00	25%
Voluntary counselling and testing	17·78	25%
Blood supply safety	8·00	10%
Weighted average cost per DALY	12·50	..

MTCT=mother-to-child transmission; STD=sexually transmitted disease.

Table 2: **Cost per DALY for hypothetical HIV prevention programme**

using our model (developed by E Marseille and J G Kahn, unpublished) the incremental cost-effectiveness of HAART compared with cotrimoxazole prophylaxis is in the range of US$600–2000 per DALY. This calculation retains the assumptions of US$350 per person-year for HAART, zero monitoring and testing costs, and no reduction in quality of life for those on HAART.

Each of these assumptions tends to overestimate the benefits, or underestimate the cost, of a HAART intervention programme. Under these overly optimistic circumstances, the cost-effectiveness of HAART is simply the annual cost of the drug divided by the annual gain in health. If we assume (again favouring HAART) that without HAART an individual would immediately die, then the gain in health is a DALY per year of treatment. Thus, the cost-effectiveness ratio is US$350 per DALY gained. The ratio between the cost-effectiveness of HAART and of prevention is then US$350:US$12·50, or 28:1.

This suggests that for every 1 life-year gained with HAART, 28 life-years could have been gained with prevention. It follows that as long as population coverage with good prevention programmes is low, money available for prevention should not be allocated to HAART. However, this assumes that the only criteria for resource allocation are captured in the simple cost-effectiveness comparison above. We do not believe that this is so. However, we also do not believe that the arguments in favour of allocating funds for HAART in sub-Saharan Africa are sufficiently compelling to alter the conclusion indicated by this crude comparison.

Examining the case for HAART

Does prevention work?

HIV control efforts in Africa have centered on prevention since the beginning of the pandemic. Since incidence has increased dramatically, it would appear that spending more on prevention is a dubious choice. We believe that prevention programmes should be assessed more frequently and more rigorously. Some, such as mass communication and social marketing programmes, are particularly difficult to assess and others have not been assessed in a sufficient number of settings. Nevertheless, as indicated by three recent review articles, an extensive body of research has shown that many prevention options are effective.[18-20] As table 1 indicates, a wide range of prevention interventions is not only effective but also cost effective. Increasing HIV incidence is not due to the failure of prevention but to the failure of prevention funding.

Does HAART make prevention more effective?

The argument that HAART makes prevention more effective is usually cited, using the case of voluntary counselling and testing (VCT). The argument is that the availability of effective treatment motivates people to come forward for VCT knowing that a positive test result is the beginning of effective care. These higher VCT uptake rates mean that more people will receive prevention counselling.[21] Investment in HAART will therefore yield an important prevention dividend. We are unaware of quantitative data supporting this argument. Our scepticism is not with the existence of such an effect, but with the strength of it. For investment in HAART to be as efficient as investing directly in prevention, about 2·1 cases of HIV would need to be averted as a result of making HAART available for each person-year of HAART provided. It seems extremely unlikely that HAART would yield prevention dividends approaching that magnitude. Again, even the annual 2·1 cases per year figure assumes no increase in risk behaviour on the part of HIV-negative individuals of the type seen in San Francisco and elsewhere in the USA since 1997.[22]

Does treatment focus the world's attention on HIV more effectively than would prevention?

The call for HAART has dramatically raised the perceived degree of HIV resources needed to have an impact on the epidemic. However, for investment in HAART to produce more benefits than investment in prevention alone, the hypothesis that HAART will leverage more funds must be correct in the extreme (table 3). For example, let us consider HIV funding in a hypothetical country that is initially spending $100 million annually on prevention only and generating 8 million DALYs as a result (100 million/$12·5 per DALY=8 million). In the first scenario, funding triples to $300 million and this sum is evenly divided between prevention and HAART. The extra $200 million spent per year generates an additional 4 428 571 DALYs. (US$150 million/US$350 per DALY for HAART plus US$100 million/US$12·50 per DALY for prevention=12 428 571 DALYs. Deduction of 8 million DALYs of the base cases leaves 4 428 571 additional DALYs saved.) Alternatively, the same gain in DALYs could be generated by spending only an additional $55 million if all of it were allocated to prevention (scenario II). If the goal is to minimise the loss of life from HIV, the question becomes, "Which proposal is more likely to be implemented, spending an additional $55 million on prevention alone, or an additional $200 million on combined HAART and prevention?" It may be the latter, but HAART advocates need to make a more compelling case. The simple assertion that spending on HAART will leverage additional funds of prevention is insufficient even if true. The vastly superior cost-effectiveness of prevention means that the HAART "leverage effect" must be large indeed. There is another possibility not mentioned by HAART proponents, namely that total HIV funding may increase but less will be allocated to prevention than would otherwise have been the case. In that case the strategy of using HAART to leverage more total funds backfires catastrophically.

	Baseline (prevention only)	Scenario I: enhanced effort prevention and HAART			Scenario II: enhanced effort prevention only
		Prevention	HAART	Total	
Annual expenditures	100 000 000	150 000 000	150 000 000	300 000 000	155 357 138
DALYs saved	8 000 000	12 000 000	428 571	12 428 571	12 428 571
Incremental cost	0	50 000 000	150 000 000	200 000 000	55 357 138
Incremental DALYs	0	4 000 000	428 571	4 428 571	4 428 571

Table 3: **Example of possible enhanced spending on treatment and prevention versus enhanced spending on prevention only**

Can HAART have a preventative effect?

That both prevention and HAART can prevent orphanhood and keep workers productive is another arguement. Even after discounting the value of these future benefits to the present, prevention is more cost- effective in maintaining the health of adults than is HAART. It is therefore equivalently more cost effective in preventing orphanhood and in maintaining workforce productivity.

Will perfecting the delivery of HAART force long-needed investment in health-care infrastructure?

The lack of proper infrastructure for delivering and monitoring complex antiretroviral regimens is part of a systemic failure in many sub-Saharan African countries to reliably deliver even basic diagnostic services and medications. Because obtaining antiretroviral medications is important for so many, it will generate the political consensus needed to upgrade the health-care system across the board. The managerial skills needed to keep antiretroviral drugs in stock, to minimise diversion, to confirm that they are administered to those who can use them, and to monitor adherence and side-effects, are the same types of skills needed to assure that other important programmes such as safe motherhood packages, malaria, tuberculosis, and sexually-transmitted disease control and diarrhoeal disease treatment are delivered effectively and consistently. Therefore, investing in the infrastructure needed to deliver HAART will spill over into other collateral health benefits.

There are three weaknesses in this argument. First, the 28:1 relative cost-effectiveness between HAART and prevention assumes no such spending on infrastructure. If it were included, the ratio becomes still more unfavourable for HAART. The estimated $9·2 billion needed for scaled-up spending assumes spending on HAART where infrastructure is already good.[6] Additional positive external effects on infrastructure would therefore be limited. The potential for infrastructure benefits increase as HAART availability spreads to settings with inferior infrastructure, but then so do costs. Second, evidence for this imputed effect is scarce. Well-documented examples in HIV control or elsewhere in public health would strengthen the argument; we are unaware of any. Presumably, the possible system-wide benefits of a HAART programmme will depend on the details of how the programme is funded and administered in each county. Third, if positive spill-over effects accrue from strengthening the treatment infrastructure, they are likely to accrue from strengthening the prevention infrastructure too. To take one example: if antiretroviral drug-based interventions to prevent mother-to-child transmission of HIV are to succeed, they will require many of the same systems that would be needed to administer HAART to extend the lives of HIV-infected adults. These include reliable distribution, inventory control, obtaining informed consent, and monitoring for side-effects. But more important than the particular skills needed to manage drug-based interventions are the general management capabilities that will also be needed if prevention is to succeed on a wider scale. If HAART has external system-enhancing benefits then perfecting the art and technology of HIV prevention will also pay dividends in strengthening the prevention infrastructure for other (non-HIV) diseases and conditions.

Could HAART lower the risk of HIV transmission?

Recent findings from Uganda indicate that the risk of transmission within discordant couples is highly correlated with HIV viral load.[23,24] This raises hope that risk of transmission from HIV-infected individuals with viral loads suppressed by antiretroviral treatment may be lower than the risk of transmission from those who are not receiving therapy. If true, antiretroviral treatment not only controls the progression of HIV to AIDS and death but also might slow the spread of the disease in the population. In short, antiretroviral therapy might be a potent prevention option.

There are a number of reasons to suspect that the prevention benefits of HAART may be limited. First, it is possible that viral load suppressed by antiretrovirals is associated with a higher risk of transmission than is the same viral load occurring in patients who have not taken antiretrovirals. Second, a large portion of HIV transmission occurs before the appearance of symptoms and therefore before the initiation of therapy.[25] Third, even when HAART is used, and assuming it greatly reduces HIV transmission, the cost-effectiveness ratio still strongly favours prevention. This is due to the low annual probability of HIV transmission from HIV-infected individuals. In the less-developed world, for example, median survival with HIV infection is about 9 years. If the epidemic is in steady-state (ie, HIV prevalence is stable over time), each infected person must transmit one infection during their lifetime (ie, $R_0=1$). Thus, average annual HIV transmission from an HIV-infected individual is 1 divided by 9, or 0·11. This is consistent with empirical evidence from an African setting that each HIV-positive person has a 10% annual risk of infecting his or her regular partner.[24] If the natural variation in HIV infectivity associated with viral load applies to HAART-induced reductions in virus, an 80% reduction might be expected.[24] Assuming that risk during late-stage disease—when HAART use is most likely—is 0·11 infections per HIV-infected person per year, this would translate to 0·09 fewer HIV infections per HAART-treated person per year. If we generously use a value of 0·15 rather than 0·09 fewer HIV infections per HAART-year, the relative cost-effectiveness of HAART and prevention falls from 28:1 to 9·4:1. Prevention thus retains a substantial advantage. Further, because individuals receiving HAART may engage in more risky behaviour and because they are likely to live longer, the benefits from lower per-episode transmission probabilities could be offset by increases in the intensity and duration of risky behaviour.[26,27]

These dangers are not only theoretical: San Francisco has recently witnessed evidence of increased HIV incidence that may well be linked to misconceptions that HAART is equivalent to a cure and that it eliminates transmission risk by those with HAART-associated viral load reductions.[22] There is some early indication that similar dynamics might operate in less-developed countries. A recently reported 3·7% rise in HIV incidence in Brazil was attributed by the Brazilian Ministry of Health to decreased condom use in young men who have sex with men. The Health Ministry added that the decline in condom use "seemed to have started after the introduction" of antiretroviral drug therapy, which Brazil provides for free to all citizens with AIDS.[28] The added survival conferred by HAART may exacerbate these effects.

Limitations to the case for prevention

We recognise a number of limitations to this analysis. First, the analysis does not account for the value of pilot studies that assess the benefits, costs, and safety of delivering HAART in selected settings. This could have the important advantage of identifying the best means for delivering HAART in resource-poor settings. Thus, after expanded funding of prevention, HAART provision could be scaled up more rapidly, since best practices would already have been identified.

Second, we focus on the broad principles that should govern allocation of the next few billion dollars of annual HIV funding. Local exceptions will occur because the cost-effectiveness of both prevention and HAART changes with scale. Once initial economies of scale have been determined, further expansion generally means lower cost-effectiveness. At a certain point, prevention will have a less favourable marginal cost-effectiveness than HAART due to the exhaustion of easily reached target populations. In general, given the low level of prevention activities in sub-Saharan Africa, this point will only be reached after several additional billion dollars in annual prevention funding. In selected areas of some countries with relatively strong medical care delivery infrastructure and monitoring capabilities, this will occur earlier. However, as HAART programmes expand beyond the most favourable implementation settings, they too can be expected to encounter an increase in marginal costs.

Third, this analysis attempts to point to a technical optimum based on efficiency criteria. In some areas, such criteria may be trumped by other considerations. There may be communities in which expectations and demand for HAART are so high that little progress in prevention and in non-HAART treatment can proceed without at least some provision of HAART as well. Finally, our point estimates for the average cost-effectiveness of prevention is rough and the cost of HAART has dropped dramatically during the past year. Less favourable estimates of prevention efficiency and lower prices of HAART imply a smaller difference in cost-effectiveness. However, if HAART prices dropped by another 50%, still ignoring the non-drug costs of delivering this therapy, and prevention costs doubled to an average of $25 per DALY, there would still be a 7:1 differential in cost-effectiveness favouring prevention.

Prevention and the rule of rescue

We believe other reasons exist to advocate the primacy of prevention. As the price drops, the pressure to spend money on HAART may become almost irresistible, for the best of humanitarian reasons. As will be discussed in more detail below, the "rule of rescue" dictates that more resources will be made available for identified sufferers than for present or future sufferers who are statistical abstractions. For this reason it is perhaps inevitable that more will be spent for treatment than is optimum (ie, more than would result in the lowest loss of life in the long-term). Thus, when the rule of rescue does not govern decisions, we have an added imperative to choose prevention.

Moreover, treatment has a stronger political appeal than prevention in general. Politicians would usually prefer to point to living individuals whose lives they can claim to have saved, than to point to a line on a graph representing future deaths averted because of their support of prevention. Those who benefit from prevention cannot be sure that they in fact benefited as individuals and are therefore less likely to be grateful (and to show their gratitude at the ballot box) than those who know they would have died if not for treatment. Due to the long incubation period during which the infected are asymptomatic, the benefits from prevention can be detected only starting 5–7 years after programme initiation. This is too distant a horizon to matter to most politicians. These are powerful forces and have much to do with the typical imbalance of treatment over prevention in general in both the developing and the industrialised world. In the face of these political dynamics, the case for the primacy of prevention must be stated clearly and repeatedly by donor agencies and other actors who are relatively removed from these dynamics.

But is it ethical?

There exists an ethical imperative based on principles of simple justice for the rich countries to mount an effective response to the HIV pandemic. This should include scaled-up prevention, treatment of opportunistic infections, care for the ill and for orphans, and the provision of HAART wherever and whenever this can be done safely. Based on the current actions of the OECD countries, it is sensible to assume that a fully scaled-up response is at least a few years away. It is also conceivable that a response will never occur at the necessary scale. In the meantime, is withholding HAART justified by the more efficient allocation of funds to prevention which benefits unknown individuals in the future? We believe that it is not only justified but also required.

The rule of rescue dictates the use of effective resources when they are available.[29] It does not consider the wisdom of their application in economic or comparative cost-effectiveness terms. If treatment, irrespective of cost, will benefit the patient then it is to be provided. The pressure to intervene is predictably intensified when the patient is an identified individual, as contrasted with an unidentified "statistical" patient. In either case, however, denying potentially beneficial treatment to any person is generally viewed as morally repugnant.

Nonetheless, circumstances exist when ethically defensible decisions are made to deny or limit such treatment. The classic situation occurs in wartime and natural disasters in which a triage process determines how limited resources will be allocated. Now, for perhaps the first time in history, we must decide whether economic reality will permit an informed debate about rationing that could result in millions of patients receiving supportive care, but not treatment, to prevent many more millions from becoming afflicted with the disease. The allocation of resources, the development of a just health-care system, and the adjudication of the rights and claims of competing groups "are and will be the important moral problems of the future".[30] Indeed, these are the present moral issues facing HIV policy makers in sub-Saharan Africa.

Of all the ethical principles relevant to an analysis of resource allocation decisions, justice is the most important—particularly when confronting an HIV pandemic that disproportionately afflicts the impoverished and politically disenfranchised. Invariably, the economically advantaged will obtain treatment, so how can a system be designed that does not discriminate based on financial status? In the short-term at least, it cannot. But it is also untenable to ignore powerful evidence about the superior cost-effectiveness of HIV prevention over HAART, and to refuse to participate in a difficult and painful debate. This debate, if joined in good faith, could save the lives of millions.

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