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Potential cost-effectiveness of community availability of tenofovir, lamivudine, and dolutegravir for HIV prevention and treatment in east, central, southern, and west Africa: a modelling analysis

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Summary

Background Post-exposure prophylaxis (PEP) offers protection from HIV after condomless sex, but is not widely available in a timely manner in east, central, southern, and west Africa. To inform the potential pilot implementation of such an approach, we modelled the effect and cost-effectiveness of making PEP consisting of tenofovir, lamivudine, and dolutegravir (TLD) freely and locally available in communities without prescription, with the aim of enabling PEP use within 24 h of condomless sex. Free community availability of TLD (referred to as community TLD) might also result in some use of TLD as pre-exposure prophylaxis (PrEP) and as antiretroviral therapy for people living with HIV.

Methods Using an existing individual-based model (HIV Synthesis), we explicitly modelled the potential positive and negative effects of community TLD. Through the sampling of parameter values we created 1000 setting-scenarios, reflecting the uncertainty in assumptions and a range of settings similar to those seen in east, central, southern, and west Africa (with a median HIV prevalence of 14·8% in women and 8·1% in men). For each setting scenario, we considered the effects of community TLD. TLD PEP was assumed to have at least 90% efficacy in preventing HIV infection after condomless sex with a person living with HIV.

Findings The modelled effects of community TLD availability based on an assumed high uptake of TLD resulted in a mean reduction in incidence of 31% (90% range over setting scenarios, 6% increase to 57% decrease) over 20 years, with an HIV incidence reduction over 50 years in 91% of the 1000 setting scenarios, deaths averted in 55% of scenarios, reduction in costs in 92% of scenarios, and disability-adjusted life-years averted in 64% of scenarios with community TLD. Community TLD was cost-effective in 90% of setting scenarios and cost-saving (with disability-adjusted life-years averted) in 58% of scenarios. When only examining setting scenarios in which there was lower uptake of community TLD, community TLD is cost-effective in 92% of setting scenarios.

Interpretation The introduction of community TLD, enabling greater PEP access, is a promising approach to consider further in pilot implementation projects.

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Introduction

Despite substantial progress in diagnosing people living with HIV and enabling them to take virally suppressive antiretroviral therapy (ART), HIV incidence is high in many parts of east, central, southern, and west Africa, with approximately 860 000 new infections in 2021.[1] Oral pre-exposure prophylaxis (PrEP) has the potential to reduce HIV incidence, but studies conducted in this region on the use of oral PrEP have reported low continuation and adherence.[2–4] The expected introduction of long-acting injectable cabotegravir PrEP in this region will provide a highly effective alternative option to people who are unable to adhere to the daily pill-taking regimen of oral PrEP.[5] However, it will take some time for this injectable PrEP to become widely available and whether it can be delivered in a risk-informed way at scale in a cost-effective manner is yet to be fully established.[6,7] In addition, all PrEP, by definition, relies on the anticipation of having condomless sex, and often the risk of HIV might not be perceived until exposure to it has occurred. For a person not on PrEP, post-exposure prophylaxis (PEP), in the form of a three-drug antiretroviral drug regimen ideally started within 24 h after condomless sex, offers protection from HIV,[8] but is generally not available outside clinical settings in east, central, southern, and west Africa, making timely access challenging. We have proposed making the PEP regimen of tenofovir, lamivudine, and dolutegravir (TLD) widely, freely, and discreetly available in communities without needing a prescription (along with condoms, HIV self-test kits, and emergency contraception), alongside community

Research in context

Evidence before this study

Post-exposure prophylaxis (PEP), in the form of a three-drug antiretroviral drug regimen, ideally started within 24 h after condomless sex, offers protection from HIV but is generally not available outside clinical settings in east, central, southern, and west Africa, making timely access challenging. We propose making tenofovir, lamivudine, and dolutegravir (TLD) widely and freely locally available in communities without prescription (community TLD). There are many potential positive and negative effects, which can be modelled. We searched Web of Science on June 16, 2023, using the terms "post-exposure prophylaxis" AND "HIV*" AND "model*" for articles in English and identified no modelling studies of easy-access TLD PEP in Africa.

Added value of this study

We modelled the potential positive and negative effects of community TLD, incorporating uncertainty over assumptions and variability between settings. The potential beneficial effects of making TLD widely available that we modelled included a higher PEP or pre-exposure prophylaxis (PrEP) prevention coverage for episodes of condomless sex in people who are HIV negative, and a greater likelihood of people living with HIV being on antiretroviral therapy (ART). The potential negative effects included: (1) the absence of an initial and 3-month HIV testing in some people taking PrEP and PEP, meaning some people who have undiagnosed HIV would be taking TLD guided by sexual risk when it should be taken continuously, with a possible increased risk of resistance; (2) the possible lower uptake of long-acting injectable cabotegravir PrEP because of the easier access to TLD PEP or PrEP; (3) an increase in the proportion of people on ART who are not under care and not monitored with viral load testing or given adherence counselling, or receiving care for advanced HIV disease as indicated; (4) an increased risk of immune response inflammatory syndrome in people with advanced HIV and other concurrent infections starting ART without clinical assessment; and (5) some use of TLD in people without HIV and without being at risk for HIV, which results in some drug waste and possibly unnecessary drug toxicity. Although there is uncertainty, our modelling suggests that community TLD is likely to reduce HIV incidence and be cost-effective, thus leading to population health benefits.

Implications of all the available evidence

There is a case for piloting the implementation of the community TLD approach to enable PEP access in Africa. One hurdle to such pilot studies will be to ensure that TLD PEP can be made available without prescription, and regulatory support will be required for this.

ownership and education, to enable PEP use within 24 h of condomless sex.[9]

Providing unrestricted access to TLD would mean some people might use TLD as PrEP or as treatment without an ongoing formal engagement with the health-care system. Therefore, the net effect on health outcomes are uncertain. The potential beneficial effects of making TLD widely available locally with community ownership and education (hereafter referred to as community TLD) include a higher PEP and PrEP prevention coverage for episodes of condomless sex in people who are HIV negative, and a greater likelihood of people living with HIV being on ART. The potential negative effects include: (1) the absence of HIV testing initially and once every 3 months in some people taking PrEP and PEP, meaning some people would have undiagnosed HIV and hence would be taking TLD according to sexual risk rather than continuously, with a possible increased risk of resistance; (2) a possible lower uptake of long-acting injectable cabotegravir PrEP due to the easier access to TLD PEP and PrEP; (3) an increase in the proportion of people on ART who are not under clinical supervision and not monitored with viral load testing or given adherence counselling, or provided care for advanced HIV disease; (4) an increased risk of immune response inflammatory syndrome in people with advanced HIV and other concurrent infections starting ART without clinical assessment; and (5) some use of TLD in people without HIV and without being at risk for HIV, which results in some drugs being wasted and possible unnecessary drug toxicity.

Although innovative approaches to the community delivery of self-testing kits for HIV and ART, oral PrEP, and PEP have been and are being studied,[10–14] the unrestricted access that we propose has not, to our knowledge, been implemented in any region of east, central, southern, and west Africa. Pilot implementation studies with process evaluation would be needed before a full implementation is made, to enable an understanding of the contexts in which community TLD is adopted as local policy, made available widely and discreetly, and used by community members. In anticipation of such studies, we built upon an existing individual-based model (the HIV Synthesis model) to provide a framework for quantifying the net effects of such an approach at a population level, including accounting for costs.

Methods

Model structure and setting scenarios

HIV Synthesis is an individual-based simulation model[15–17] for which each model run generates a simulated population of adults with variable values on each person updated every 3 months, including age, sex, primary and non-primary condomless sex partners, whether currently a female sex worker, having had an HIV test, male circumcision status, the presence of sexually transmitted

infections other than HIV, and the use of PrEP and PEP. For people in the simulated population who are HIV positive, we modelled viral load, CD4 cell count, use of specific antiretroviral drugs, adherence, and drug resistance. Further methods are detailed in appendix 1 (pp 5–108).

Through the sampling of parameter values (appendix 1 p 70), we created 1000 setting scenarios reflecting uncertainty in the model assumptions and a range of settings similar to those seen in east, central, southern, and west Africa. The characteristics of these setting scenarios are described in table 1 and compared with observed data from the Population Health Impact Assessment project.

See **Online** for appendix 1

Policy comparison

For each setting scenario, we compared outcomes from 2024 between two policies: the continuation of existing

For **Population Health Impact Assessment surveys** see https://phia.icap.columbia.edu/

	Model median (90% range)	Examples of observed data by country in east, central, southern, and west Africa*									
		Zimbabwe	Tanzania	Uganda	Lesotho	Eswatini	Ethiopia	Malawi	Namibia	Zambia	Cameroon	Côte d'Ivoire
HIV prevalence in people aged 15–49 years	14·8% (5·6–30·9%) in women and 8·1% (3·3–17·2%) in men	2016: 16% in women and 11% in men; 2020: 15% in women and 9% in men	2017: 6% in women and 3% in men	2017: 7·4% in women and 3·8% in men	2017: 30% in women and 19% in men; 2020: 28% in women and 16% in men	2017: 34% in women and 19% in men; 2021: 32% in women and 16% in men	2018: 4·0% in women and 1·7% in men	2020: 10% in women and 6% in men	2017: 15% in women and 8% in men	2016: 14% in women and 8% in men	2017: 5% in women and 2% in men	2018: 4% in women and 1% in men
HIV incidence per 100 person-years in people aged 15–49 years	0·61 (0·25–1·73) in women and 0·38 (0·14–0·97) in men	2016: 0·57 in women and 0·30 in men; 2020: 0·67 in women and 0·23 in men	2017: 0·34 in women and 0·14 in men	2021: 0·42 in women and 0·21 in men	2017: 1·31 in women and 1·05 in men; 2020: 0·81 in women and 0·33 in men	2017: 1·73 in women and 0·85 in men; 2021: 1·45 in women and 0·20 in men	..	2020: 0·31 in women and 0·15 in men	2017: 0·66 in women and 0·15 in men	2016: 1·00 in women and 0·28 in men	2017: 0·40 in women and 0·08 in men	2018: 0·03 in women and 0·03 in men
Proportion of people diagnosed as HIV positive of all people with HIV	91% (82–97%) in women and 82% (71–92%) in men	2016: 80% in women and 72% in men; 2020: 88% in women and 84% in men	2017: 65% in women and 52% in men	2021: 83% in women and 76% in men	2020: 91% in women and 98% in men	2021: 95% in women and 92% in men	2018: 83% in women and 70% in men	2016: 80% in women and 72% in men; 2020: 90% in women and 85% in men	2017: 83% in women and 71% in men	2016: 73% in women and 69% in men	2017: 58% in women and 51% in men	2018: 54% in women and 40% in men
Proportion of people diagnosed as HIV positive on ART	96% (83–99%) in women and 94% (78–98%) in men	2016: 89% in women and 88% in men; 2020: 98% in women and 96% in men	2017: 95% in women and 90% in men	2016–17: 90% in women and 85% in men; 2021: 97% in women and 95% in men	2017: 92% in women and 92% in men	2016–17: 88%in women and 90% in men; 2021: 98% in women and 96% in men	2018: 96% in women and 99% in men	2016: 93% in women and 89% in men; 2020: 98% in women and 97% in men	2017: 96% in women and 94% in men	2016: 87% in women and 88% in men	2017: 93% in women and 94% in men	2018: 94% in women and 85% in men
Proportion of all people who were HIV positive with a viral load of less than 1000 copies per mL	76% (61–87%)	2016: 60%; 2020: 76%	2017: 52%	2017: 60%; 2021: 75%	2017: 68%; 2020: 81%	2017: 73%; 2021: 89%	2018: 70%	2016: 68%; 2020: 87%	2017: 77%	2016: 59%	2017: 47%	2017–18: 40%
Prevalence of HIV viral load more than 1000 copies per mL among all adults	3·0% (1·1–7·2%)	2016: 5·7% (in those aged 15–64 years); 2020: 3·1% (in those aged 15 years or older)	2·8% in women aged 15–64 years; 2·1% in men aged 15–64 years	2021: 1·6% in women and 1·3% in men	2018: 8·3% (in those aged 15–59 years); 2020: 4·3% (in those aged 15–59 years)	2017: 7·3% (in those aged 15 years or older); 2021: 2·7% (in those aged 15 years or older)	2018: 0·9%	2016: 3·4% (in those aged 15–64 years); 2020: 1·2% (in all ages)	2017: 2·8% (in those aged 15–64 years)	2016: 4·8% (in those aged 15–59 years)	2017: 2·0%	2018: 1·7% (in those aged 15–64 years)
Of people on ART, proportion with a viral load of less than 1000 copies per mL	95% (85–99%) in women and 92% (79–98%) in men	2016: 88% in women and 84% in men; 2020: 91% in women and 89% in men	2017: 83% in women and 89% in men	2021: 93% in women and 91% in men	2020: 92% in women and 90% in men	2021: 96% in women and 97% in men	2018: 86% in women and 91% in men	2016: 92% in women and 90% in men; 2020: 97% in women and 97% in men	2017: 92% in women and 90% in men	2016: 90% in women and 88% in men	2017: 80% in women and 81% in men	2018: 77% in women and 63% in men

Model median is the median across all 1000 setting scenarios for all countries in east, central, southern, and west Africa. Based on 1000 setting scenarios. ART=antiretroviral therapy. *All observed data are from Population Health Impact Assessment surveys. Note that we show national data by each country for the observed data, but setting scenarios reflect sub-settings within countries as well as countries as a whole. Of setting scenarios, those with an HIV incidence in those aged 15–49 years of less than 0·15 per 100 person-years or an HIV prevalence in those aged 15–49 years of more than 27% in mid-2022 were excluded.

Table 1: **Description of setting scenarios in 2022 compared with observed data**

oral two-drug PrEP availability at the levels at the start of 2024 and the scale-up of long-acting injectable cabotegravir PrEP only, and the same PrEP implementation with the addition of community TLD.Without community TLD availability, PEP use was assumed to be negligible. Before describing the implementation of community TLD, we first describe the modelling of PrEP (appendix p 31). Throughout this description of the methods, the distributions for the parameters shown in the appendix (p 70) reflect the degree of uncertainty.

Any PrEP use was assumed to be during a 3-month period in which the person had condomless sex and not used at other times. We considered that there was an indication for PrEP in any 3-month period if the person had condomless sex with at least one non-primary partner, or if the primary partner might have unsuppressed HIV. The extent to which PrEP use corresponds to periods of having condomless sex (ie, is risk-informed)[16] is uncertain, but some studies of HIV incidence in people on PrEP support this notion.[18,19] We did not explicitly distinguish between whether PrEP use was event-driven or continuous. Each person had, for each form of PrEP (oral or injectable), an individual value on a scale of 0–1—conveying how willing they would be to take that form of PrEP if and when they had an indication to take PrEP (randomly assigned, but accounting for the fact that people are more willing to take cabotegravir injectable than oral PrEP, so the values on average were higher for cabotegravir injectable). The willingness to take PrEP has to be above a lower threshold (0·2) for them to consider taking that form of PrEP. If a person began taking PrEP, they would begin taking the form of available PrEP for which they had the highest willingess value. Some simulated people were considered to live in circumstances that made them unable to access clinical services, and thus would not have access to HIV testing or PrEP (in the absence of community TLD introduction). Oral PrEP and long-acting injectable cabotegravir PrEP were assumed to have either a 90% efficacy (with a 20% probability of this value per setting scenario) or a 95% efficacy (with an 80% probability of this value per setting scenario), with the effectiveness of oral PrEP dependent on adherence (approximately 80% of people were assumed to have had an adherence of more than 80%). The effectiveness of long-acting injectable cabotegravir PrEP was the same as the efficacy.

When considering community TLD, our model aimed to incorporate all the potential positive and negative effects described earlier. With community TLD introduction (appendix p 68), TLD would be available to any person who felt that they had a potential past or future risk of exposure to HIV, regardless of their ability to access formal clinic services. A key value of PEP is that it is used according to specific risks, and so avoids the problem that PrEP use has, in that a person is unable to judge if a risk will occur, and thus PEP use by definition is risk-informed. Whether TLD is used as PEP or PrEP was established by sampling. The efficacy of TLD as PEP was assumed to be 90% (with an 80% probability of being chosen for a given setting scenario) or 95% (with a 20% probability of being chosen for a given setting scenario). TLD used as oral PrEP was assumed to have the same efficacy as two-drug oral PrEP (tenofovir and emtricitabine). The effectiveness of PEP was dependent on adherence as well as efficacy, with adherence to PEP assumed to be the same as adherence to PrEP. We considered in some setting scenarios that community TLD could result in a decreased adherence (when used as PrEP or PEP) compared with if PrEP or PEP were provided in a clinical setting, or could result in an increased adherence because people would be self-motivated to take it. It was assumed by default with community TLD that there was an absence of initial and 3-month HIV testing in clinics for people with a PEP or PrEP indication, which results in some people taking PEP or PrEP when they already have undiagnosed HIV. Additionally, some people who were taking PEP or PrEP due to community TLD access might nevertheless be tested every 3 months under clinical supervision, and some might self-test. When the prevalence of an HIV viral load of more than 1000 copies per mL among all adults in a setting reaches less than a specific amount, people might not consider there to be a high enough HIV risk to warrant the use of PrEP or PEP, so in the setting scenarios we assumed that there was a 33% chance that PrEP or PEP use stopped when this prevalence was less than 0·5%, 33% chance that this was less than 1·0%, and a 33% chance that there was no such effect.

	No community TLD	Community TLD	Comparison
Percentage of people with a current PEP or PrEP indication who take PEP or PrEP	25% (10 to 43)	35% (18 to 52)	9% (3 to 16)
Percentage of people who were HIV negative aged 15–49 who were taking PEP or PrEP	1·1% (0·2 to 2·9)	1·6% (0·4 to 4·0)	0·5% (0·1 to 1·4)
Percentage of people on PEP or PrEP (oral or long-acting injectable cabotegravir) who are on long-acting injectable cabotegravir	35% (0 to 66)	29% (0 to 55)	–7% (–18 to 0)
Proportion of people on TLD PEP or PrEP who are on PEP	..	69% (47 to 90)	69% (47 to 90)
Proportion of men living with HIV on ART	79 (62 to 91)	82 (69 to 92)	3 (1 to 9)
Proportion of women living with HIV on ART	88 (75 to 95)	90 (81 to 96)	3 (0 to 8)
Proportion of people living with HIV on ART who are not attending clinic	..	14% (2 to 41)	14% (2 to 41)
Proportion of people taking TLD who are HIV negative (or HIV positive and undiagnosed) without a prevention indication	..	0·3% (0·0 to 1·6)	..

Data are mean (90% range over all setting scenarios) over 3 years. 90% ranges reflect both uncertainty in assumptions and variability between settings in east, central, southern, and west Africa, restricted to setting scenarios with an HIV incidence in 2022 of more than 0·15 per 100 person-years and a prevalence of less than 27%. The short-term effects (3 years) shown here reflect assumptions over uptake. ART=antiretroviral therapy. PEP=post-exposure prophylaxis. PrEP=pre-exposure prophylaxis. TLD=tenofovir, lamivudine, and dolutegravir.

Table 2: **Modelled implementation of community TLD across 1000 settings scenarios**

	No community TLD	Community TLD	Comparison
Proportion of people on ART with viral suppression (at 20 years)	95% (90 to 98)	94% (86 to 98)*	–1% (–5 to 0)
Proportion of all people with HIV with viral suppression (at 20 years)	81% (67 to 90)	84% (73 to 92)	3% (–4 to 13)
Prevalence of an HIV viral load of >1000 copies per mL among all adults (at 20 years)	1·7% (0·5 to 4·1)	1·2% (0·3 to 2·9)	–0·5% (–1·8 to 0·0)
HIV incidence in people aged 15–49 years (over 20 years)	0·36 (0·09 to 0·91)	0·24 (0·06 to 0·60)	–31% (6 to –57)
HIV prevalence in people aged 15–64 years (at 20 years)	5·0% (1·2 to 12·4)	3·5% (0·8 to 8·2)	–27% (5 to –46)
Prevalence of integrase inhibitor-resistant HIV among all adults aged 15–64 years (at 20 years)	0·5% (0·0 to 1·4)	0·5% (0·0 to 1·4)	0·0% (–0·2 to 0·3)
Prevalence of NRTI-resistant HIV among all adults aged 15–64 years (at 20 years)	3·2% (0·9 to 6·9)	3·1% (0·9 to 6·9)	0·0 (–0·8 to 1·1)
Deaths caused by HIV per year (over 20 years)	16 300 (5200 to 37 700)	14 900 (4800 to 31 100)	–1400 (–9300 to 4400)

Data are mean (90% range over all setting scenarios). Data are shown for all adults (people aged ≥15 years) unless otherwise specified. 90% ranges reflect both uncertainty in assumptions and variability between settings in east, central, southern, and west Africa, in the context of an adult population of 10 million. ART=antiretroviral therapy. NRTI=Nucleos(t)ide reverse transcriptase inhibitor. TLD=tenofovir, lamivudine, and dolutegravir. *90% (80 to 96) in people on ART who were not visiting the clinic when restricted to setting scenarios in which community TLD leads to lower adherence.

***Table* 3: Modelled effect of community TLD on health outcomes over or at 20 years across 1000 settings scenarios in east, central, southern, and west Africa**

We then considered the effects of community TLD on people with HIV. For people with diagnosed HIV, easier local access to treatment and an accompanying decrease in travel costs and time required to visit clinic could lead to a lower rate of treatment interruption and a higher rate of restarting ART among people who have discontinued. We modelled whether a person on ART was visiting a clinic. If they were not visiting a clinic, we assumed they were not monitored or receiving the potential benefits of enhanced adherence counselling, nor were they receiving the benefits of prevention and early diagnosis of opportunistic infections associated with the WHO advanced HIV disease package that is assumed to be available if this package is required for 80% of the people visiting a clinic. This assumption that these people were not visiting a clinic was implemented as a 25% higher death rate compared to those visiting a clinic. There is an additional absolute risk of death (which is either 0·01, 0·03, or 0·05; for each setting scenario we sampled one value) due to immune response inflammatory syndrome when starting ART with a CD4 count of less than 100 and not under clinical supervision. We also considered, in 20% of setting scenarios, a possible additional negative effect on adherence, in that the proportion of people on ART but not visiting a clinic with viral suppression is 90% compared with 95% in those visiting a clinic. People who have never tested for HIV in a clinical context might use TLD if they believe they have HIV, possibly based on the use of a self-test kit available in local communities with TLD. There could be some people who are HIV negative who start TLD because of the false positive results of a self-test kit or because they think they have HIV without testing. People taking TLD because they have HIV or think they have HIV and have not taken a test will take TLD continuously unless they interrupt. People with HIV taking TLD as PrEP (because they have not tested and are not aware of their HIV) will take it only in 3-month periods of risk. In this scenario, they would effectively be taking ART but interrupting frequently (at least until they are tested and find they are positive). People with HIV taking TLD as PEP (because they have not tested for HIV) will take it for an unspecified number of days within the 3-month period in which they had an indication to take PEP. We implemented this as being on ART with zero adherence for that 3-month period.

Cost-effectiveness analysis

The costs are detailed in the appendix (pp 90–91). 3 months of TLD use, including a 20% additional supply chain cost to cover distribution, costs US$16.[20] We did not explicitly include additional implementation costs, since we considered that those would be informed by how communities decided to implement the approach. We assumed a full 3-month cost of TLD for 3-month periods in which PEP was used. We simulated the absolute numbers of health-related events, costs, and disability adjusted life-years (DALYs) among adults for a base population of 10 million adults over a 50-year period from 2024 to 2073. We used a disability weight of 0·02 for people living with HIV without a current WHO stage 3 or 4 condition and without drug toxicity (appendix p 90). Resource use and cost were analysed from a health-care system perspective. We also calculated the net DALYs, a measure of the full health implications of the intervention being delivered by the health-care system, accounting for opportunity costs.[21] We used a cost-effectiveness threshold of $500 per DALY averted ($300 per DALY averted as a sensitivity analyses) and a 3% per annum discount rate for both costs and health outcomes to calculate net DALYs averted; if net DALYs were averted, this is equivalent to the incremental cost-effectiveness ratio being less than $500. Country-specific thresholds were uncertain but $500 averted per DALY

	No community TLD	Community TLD	Comparison
DALYs per year	2 052 000	2 039 000	−13 600 (−81 000 to 31 000)
Annual cost	US$127·8 million (54·5 to 232·4)	$109·8 million (49·3 to 193·5)	−$18·0 million (−53·2 to 1·8)
Net DALYs per year	2 308 000	2 258 000	−49 700 (−153 000 to 9000)
Percentage of setting scenarios in which HIV incidence reduced	..	..	91%
Percentage of setting scenarios in which deaths were averted	..	..	55%
Percentage of setting scenarios in which DALYs were averted	..	..	64%
Percentage of setting scenarios in which costs were saved	..	..	92%
Percentage of setting scenarios in which net DALYs were averted (ie, community TLD is cost-effective)	..	..	90%
Percentage of setting scenarios in which DALYs were averted and costs were saved	..	..	58%
Percentage of setting scenarios in which community TLD is cost effective according to PrEP or PEP uptake*			
<7%	..	..	92%
>7%	..	..	89%
Percentage of setting scenarios in which community TLD is cost-effective according to prevalence of HIV in 2024			
<8%	..	..	85%
8 to <12%	..	..	89%
≥12%	..	..	94%

Data are mean (90% range over all setting scenarios). DALYs=disability-adjusted life years. PEP=post-exposure prophylaxis. PrEP=pre-exposure prophylaxis. TLD=tenofovir, lamivudine, and dolutegravir. *Percentage of setting scenarios in which community TLD is cost-effective according to the difference in the percentage of people with a current PEP or PrEP indication who take PEP or PrEP at 3 years.

Table 4: **Effects of community TLD on DALYs and cost-effectiveness analysis over 50 years**

For the outputs on **Figshare** see https://figshare.com/articles/software/hiv_synthesis_community_tld_sas/24072609

	No community TLD	Community TLD
Clinic-based HIV testing	$12·5	$12·1
HIV self-test kits	NA	$0·4
Oral PrEP or PEP drug	$2·3*	$9·0†
Injectable PrEP drug	$2·5	$2·3
PrEP clinic visits	$4·1	$3·7
ART drug	$42·5	$37·6
Cotrimoxazole	$3·0	$1·7
ART clinic visits	$30·1	$17·1
Adherence intervention	$6·2	$6·2
Viral load tests	$8·3	$4·9
CD4 count tests	$0·2	$0·1
Treatment of WHO stage 3 and 4 conditions	$8·0	$7·6
Voluntary medical male circumcision	$1·8	$1·8
Care for children with HIV	$3·6	$2·8
Care for non-AIDS conditions before death	$2·7	$2·4
Total	$127·8	$109·8

Data are mean (US$ million per year) over 50 years. ART=antiretroviral therapy. PEP=post-exposure prophylaxis. PrEP=pre-exposure prophylaxis. TLD=tenofovir, lamivudine, and dolutegravir. *Oral PrEP, including tenofovir and emtricitabine. †TLD PEP and TLD PrEP.

Table 5: **Breakdown of discounted annual cost over 50 years**

averted was likely to be at the upper end based on evidence concerning how resources would otherwise be used.[22]

The model was coded in SAS version 9.4. The model program and programs to analyse the outputs are available on Figshare. This modelling study did not require ethical approval.

Role of the funding source

The Bill & Melinda Gates Foundation programme officer for the grant that funded this analysis had no role in the study design or interpretation or writing of this report. Other Bill & Melinda Gates Foundation staff (PE) with technical interest and experience, but no funding oversight, participated throughout the effort.

Results

The range of short-term (3-year long) effects of community TLD introduction are shown in table 2, and the equivalent 20-year outcomes are shown in the appendix (p 2). Our assumptions on the uptake of community TLD are a mean of 9% (90% range of 3–16%) higher PEP or PrEP use among people with an indication for PrEP or PEP compared with community TLD not being available, and a mean of 0·5% (0·1–1·4%) increase in the overall proportion of adults who were HIV negative taking PrEP or PEP. There was predicted to be a reduced use of long-acting cabotegravir (with a mean of 29% of all people taking PrEP or PEP at year 3 with community TLD *vs* 35% without community TLD) due to the availability of another prevention choice (TLD; albeit with lower effectiveness) that some people might prefer, which might be considered a disadvantage of community TLD.

69% (47–90%) of use of community TLD for HIV prevention was assumed to be as PEP, with the remaining proportion used as PrEP. Our assumptions meant that community TLD resulted in a mean 3% (for both women and men) increase in the proportion of people living with HIV who are on ART, with a mean 14% (2–41%) of people on ART at any point in time using community TLD rather than attending clinic, with cycling in and out of clinic attendance.

Table 3 shows outcomes over 20 years: a mean of 3% (–4 to 13%) increase in the proportion of people living with HIV who have viral suppression, a decrease of 0·5% (0·0 to 1·8%) in the prevalence of an HIV viral load of more than 1000 copies per mL among all adults at 20 years of community TLD, a 31% decrease (6% increase to 57% decrease) in HIV incidence over 20 years, and a 27% lower (5% higher to 46% lower) HIV prevalence at 20 years, decreasing from 5·0% with no community TLD to 3·5% with community TLD. There was no predicted detrimental effect on the prevalence of integrase inhibitor or nucleos(t)ide reverse transcriptase inhibitor resistance. HIV-related deaths were predicted to be reduced by a mean of 1400 per year (a 9% reduction), with deaths averted in 58% of setting scenarios over a 20 year time period.

Considering DALYs, costs, and cost-effectiveness over a 50 year time period (table 4), there was a mean of 13 600 DALYs averted per year (discounted at 3%), with DALYs being averted in 64% of setting scenarios. Overall costs were lower with community TLD than with no community TLD in 92% of setting scenarios, with $18·0 million (14% of the overall HIV budget of $127·8 million per year) savings per year over 50 years as a result of fewer people requiring ART and lower ART-related clinic visits over the long-term; the cost breakdown is shown in table 5. Net DALYs were averted with community TLD (ie, it is cost-effective) in 90% of setting scenarios, with a mean of 49 700 net DALYs averted. Although our assumptions meant that we modelled a high uptake of community TLD as PrEP or PEP, cost-effectiveness did not depend on a high uptake. When we restricted the setting scenarios with a much lower uptake of community TLD (ie, a difference in the percentage of people with a current PEP or PrEP indication who take PEP or PrEP at 3 years of <7% compared with a median of 10% overall), community TLD was cost-effective in 92% of setting scenarios (table 4). The percentage of setting scenarios in which community TLD was cost-effective according to HIV prevalence in 2024 is also shown in table 4.

Table 6 shows the influence of parameter values relating to community TLD on the deaths and DALYs averted and on cost-effectiveness. The deaths and DALYs averted were mainly sensitive to the effect of community TLD on adherence to PrEP (or PEP) and on adherence to ART beyond the effect of an absence of viral load monitoring and targeted enhanced adherence counselling in people self-taking ART. Even with a lower adherence, community TLD was still cost-effective in most setting scenarios. For our analyses, we used a cost-effectiveness threshold of $500 per DALY averted. When instead using a threshold

	Parameter distribution	Percentage of setting scenarios over 50 years*		
		Community TLD averts deaths	Community TLD averts DALYs	Community TLD is cost-effective
prob_prep_pop_wide_tld†				
0·05	50%	58%	68%	90%
0·10	50%	51%	61%	90%
prep_dependent_prev_vg1000‡				
No	33%	57%	63%	84%
Yes, when prevalence of an HIV viral load of >1000 copies per mL among all adults is 1·0%	33%	59%	64%	94%
Yes, when prevalence of an HIV viral load of >1000 copies per mL among all adults is 0·5%	33%	49%	64%	91%
prop_pep§				
0·5	33%	60%	67%	91%
0·7	33%	55%	65%	90%
0·9	33%	50%	61%	89%
pep_efficacy¶				
0·90	80%	54%	64%	90%
0·95	20%	56%	64%	91%
prep_oral_efficacy‖				
0·90	20%	49%	63%	89%
0·95	80%	56%	64%	90%
pop_wide_prep_adh_effect**				
Effectiveness × 0·75	10%	41%	51%	78%
Effectiveness × 0·90	10%	48%	57%	89%
No effect	60%	55%	65%	91%
Effectiveness × 1/0·90	10%	65%	74%	96%
Effectiveness × 1/0·75	10%	65%	70%	90%
rr_interrupt_pop_wide_tld††				
1/1·5	30%	55%	67%	91%
1/2·0	30%	59%	68%	93%
1/3·0	30%	54%	62%	89%
1/5·0	10%	51%	60%	87%
rr_return_pop_wide_tld‡‡				
1·5	25%	51%	61%	92%
2·0	25%	48%	60%	87%
3·0	25%	57%	64%	90%
5·0	25%	63%	72%	90%
pop_wide_tld_selective_hiv§§				
10 times	33%	58%	67%	89%
30 times	33%	55%	66%	89%
100 times	33%	51%	59%	92%
prob_tld_hiv_concern¶¶				
0·0000	33%	58%	64%	91%
0·0001	33%	55%	67%	90%
0·0010	33%	51%	61%	89%

(Table 6 continues on next page)

	Parameter distribution	Percentage of setting scenarios over 50 years*		
		Community TLD averts deaths	Community TLD averts DALYs	Community TLD is cost-effective
(Continued from previous page)				
prob_test_pop_wide_tld_prep||||				
0·10	50%	55%	65%	90%
0·25	50%	54%	64%	90%
prob_onartvis0_0_to_1* **				
0·02	25%	62%	68%	86%
0·05	25%	50%	61%	91%
0·10	25%	52%	64%	93%
prob_onartvis0_1_to_0* **				
0·005	25%	55%	67%	88%
0·010	25%	51%	60%	91%
0·030	25%	55%	66%	93%
0·050	25%	58%	64%	88%
artvis0_lower_adh†††				
No effect	80%	58%	67%	92%
Lower adherence	20%	44%	50%	81%
death_r_iris_pop_wide_tld‡‡‡				
0·01	33%	56%	63%	91%
0·03	33%	54%	63%	87%
0·05	33%	54%	66%	92%
adh_pattern§§§				
1	5%	71%	81%	93%
2	75%	55%	65%	92%
3	10%	48%	57%	87%
4	5%	52%	61%	82%
5	3%	43%	49%	74%
6	1%	63%	38%	100%
7	1%	0%	25%	63%

Parameter names are from hiv_synthesis_community_tld.sas. Parameter names are in the appendix (p 70). ART=antiretroviral therapy. DALYs=disability-adjusted life-years. PEP=post-exposure prophylaxis. PrEP=pre-exposure prophylaxis. TLD=tenofovir, lamivudine, and dolutegravir. *DALYs and costs discounted at 3% per year. †The probability of starting TLD PEP or PrEP in a given 3-month period for a person who is willing to take PrEP and has an indication to take PEP or PrEP, when community TLD access is available. ‡When the prevalence of an HIV viral load of more than 1000 copies per mL among all adults reaches less than a specific amount, people might not consider there to be a high enough risk of HIV to warrant the use of PrEP or PEP; this parameter identifies whether there is such a threshold and, if so, what it is. §Under community TLD access, the proportion of PEP or PrEP use in people with an indication to use PEP or PrEP that is being used as PEP rather than PrEP. ¶The efficacy of PEP for HIV prevention (ie, with full adherence). ||The efficacy of oral PrEP for HIV prevention (ie, with full adherence). **The effect of community TLD without clinical supervision on adherence, hence this parameter is termed prevention effectiveness. ††The degree to which the rate of interruption of ART is reduced with community TLD access. ‡‡The degree to which the rate of restarting ART in people who had discontinued is reduced with community TLD access. §§People who have never tested for HIV in a clinical context might use TLD if they believe they have HIV, possibly based on the use of a self-test kit available with community TLD. There could be some people who are HIV negative who start TLD because of a false positive result from a self-test kit or because they think they have HIV without testing. This parameter indicates how many times greater the probability is of a person with HIV starting TLD compared with a person without HIV. ¶¶The probability per 3 months of a person who has never tested for HIV but has had at least one short-term condomless sex partner in the past starting TLD. This parameter is for a person with HIV; the probability is pop_wide_tld_selective_hiv times lower for a person without HIV. ||||Probability of people who are taking PEP or PrEP because of community access getting tested every 3 months under clinical supervision. ***Probability that a person who is on ART under clinical care will transition to self-taking ART (and the reverse) and hence will not be monitored or receive any benefits of enhanced adherence counselling. †††The effect on adherence of being on ART but not under clinical monitoring, beyond the effects of not having viral load tested and thus not having enhanced adherence counselling if viral load is more than 1000. ‡‡‡Additional absolute risk of immune response inflammatory syndrome when starting ART with a CD4 count of less than 100 and not under clinical supervision. §§§Pattern of adherence to PEP or PrEP and ART in the population.

Table 6: **Parameters by values relating to community TLD access as predictors of deaths and DALYs averted, and cost-effectiveness across 1000 setting scenarios**

value of $300 per DALY averted, the number of net DALYs averted per year increased to 73 700.

Finally, to show the short-term budget impact of community TLD introduction, we calculated the undiscounted mean annual difference in costs over 5 years with and without community TLD introduction. The costs were $229·9 million total per year without community TLD and $217·5 million per year with community TLD. These cost savings, together with the approach leading to less DALYs being incurred, means it is likely that additional resources can be invested to support the implementation and uptake of community TLD in addition to its direct costs.

Discussion

Our results suggest that introduction of community TLD, enabling much wider and more timely PEP access, might well be cost-effective and lead to population health benefits. The approach can be piloted in communities and the findings analysed within the modelling framework that we present. Although our results also indicate a potentially high effect of community TLD on HIV incidence, this finding, unlike the cost-effectiveness, depends on the amount of use of community TLD. The main reason that the substantial reduction in incidence does not translate to an equally substantial reduction in deaths is the positive outcomes of people with HIV on treatment, so many people with HIV do not die of HIV-related causes. Community TLD was defined as cost-effective if it resulted in reduced net DALYs. In some setting scenarios, net DALYs were averted because of the reduction in overall costs, but DALYs were not, which meant that the cost savings would result in more DALYs averted elsewhere in the health-care system than were incurred with community TLD. There was not predicted to be any increase in overall amounts of integrase inhibitor or nucleos(t)ide reverse transcriptase inhibitor resistance. The framework we have developed can potentially be adapted to account for any newly identified health effects as further evidence emerges in future, especially from the communities in which the approach is first implemented. Although there have been modelling studies of PEP in east, central, southern, and west Africa,[23] we did not identify any that evaluated the potential positive and negative effects of community TLD.

We propose that pilot implementation studies should be done, examining a policy of having packs of TLD freely and discreetly available in a similar manner to condom access in public places, along with free self-test kits and post-coital contraception. TLD has a shelf life of 36 months and does not require refrigeration. Community education, in addition to the existence of packs of TLD in public places, would enhance PEP and PrEP awareness.[24] For people who have HIV and are accessing TLD without attending a clinic, there would be advice to attend clinic when possible, in particular when there is an onset of any symptoms. We would argue that implementation in the community should be full-scale

free and easy local access to TLD from initiation, so that community members become comfortable with the full access to TLD when needed. One hurdle will be to ensure that TLD PEP can be made available without prescription and regulatory support will be required for this move. Accompanying this pilot implementation there would be monitoring and evaluation (conditional on this not affecting people having easy and discreet access to TLD) to assess the quality of implementation, reach, adoption, context of use, maintenance, unused drug, and costs.

In our model, the effects of ART on viral load, CD4 count, and subsequent risk of AIDS and death were determined by adherence and the activity of the regimen, which is affected by any viral resistance. Assumptions on the risk of drug resistance emergence to dolutegravir have been informed by multiple studies on virological failure and drug resistance among those with virological failure. Thus, we accounted for the negative effects on integrase inhibitor resistance emergence of there being any tendency for community TLD to lead to lower ART adherence. It would be important that, as part of any pilot implementation, resistance to dolutegravir should be considered. However, this analysis is from the health system perspective. It would be premature to implement an intervention in pilot sites to evaluate its effect before meaningful community engagement to develop an approach that is responsive to the needs of intended users.

We calculated DALYs as a measure of health. For HIV prevention interventions it has become increasingly important to consider the disability weight associated with living with HIV. This is because high amounts of successful use of treatment mean that many people with HIV will not die from the infection. We used a disability weight of 0·02 for living with HIV without a current WHO stage 3 or 4 condition and without drug toxicity. This number is lower than the Global Burden of Disease disability weight of 0·078 for people on ART.[25] Had we used a higher weight, the cost effectiveness of community TLD would have been greater.

The main limitation of our study is that there are no data to inform the effects of community TLD implementation, so we had to consider a wide range of possible effects, leading to high uncertainty in the predicted overall health effects. For example, one key influential factor that is uncertain is the use of community TLD by people with diagnosed HIV, and whether this negatively or positively influences ART coverage and adherence. Likewise, there is uncertainty over PEP uptake and adherence and the extent to which its use aligns with the actual risk associated with a given sexual exposure. Effective adherence to PEP could be poorer than adherence to oral PrEP because of the need to initiate PrEP rapidly after a sexual risk, but could also be greater because PEP involves less pill-taking and is linked to a specific perceived exposure. For these reasons, this should be considered an illustrative analysis that makes the case for implementation studies, rather than evidence in itself for benefits of community TLD.

In summary, the introduction of community TLD, enabling greater PEP access, is a promising approach to consider further in pilot implementation projects. We urge implementers and funders to consider such pilot studies.

Contributors

MS, JRH, CG, KS, CFG, PE, AR, JDL, ES, and FC contributed to the creation of the concept of community tenofovir, lamivudine, and dolutegravir (TLD), contributed to the approach to modelling, commented on the modelling results and the manuscript, and read and approved the final version of the manuscript for publication. PR contributed to the creation of the concept of community TLD, contributed to the approach to modelling (particularly the cost-effectiveness analysis), commented on the modelling results and the manuscript, and read and approved the final version of the manuscript. JS, LB-M, and VC contributed to the creation of the concept of community TLD, contributed to the approach to the modelling and model coding and running, commented on the modelling results and the manuscript, read and approved the final version of the manuscript, and accessed all programmes and model outputs. ANP contributed to the creation of the concept of community TLD, contributed to the approach to modelling and model coding and running, commented on the modelling results and manuscript, read and approved the final version of the manuscript, accessed all programmes and model outputs, and wrote the first draft of the manuscript. JS, LB-M, VC and ANP verified the model results. All authors had full access to model results and had final responsibility for the decision to submit for publication. ANP, VC, LB-M, and JS accessed and verified the data.

Equitable partnership declaration

The authors of this paper have submitted an equitable partnership declaration (appendix 2). This statement allows researchers to describe how their work engages with researchers, communities, and environments in the countries of study. This statement is part of *The Lancet* journals' broader goal to decolonise global health.

See **Online** for appendix 2

Data sharing

The model programme and programmes to analyse the outputs are available on Figshare (https://figshare.com/articles/software/hiv_synthesis_community_tld_sas/24072609).

Declaration of interests

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