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Chapter 4

Benefits of early antiretroviral treatment initiation outweigh risk of transmitted HIV drug resistance: a modeling study of two East African settings

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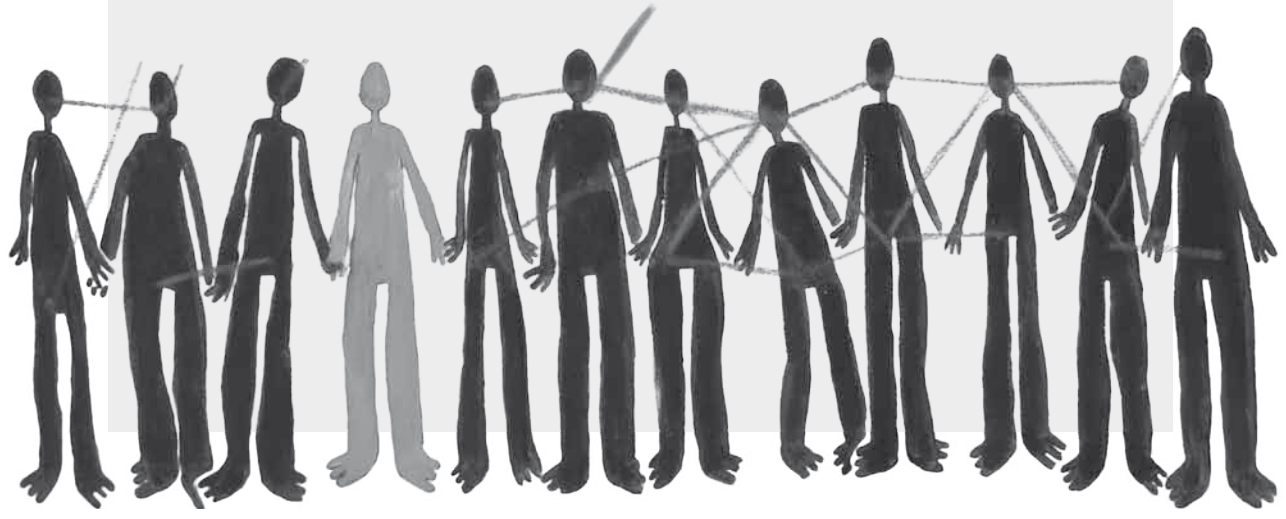
Submitted



ABSTRACT

Background

Earlier antiretroviral therapy (ART) initiation can reduce the number of incident HIV infections in a population. This benefit can, however, be offset by increased transmitted drug resistance (TDR). We compared the preventative benefits of reducing incident infections with the potential increases in TDR in East Africa.

Methods

A compartmental deterministic model was constructed and parameters were chosen to represent Kampala, Uganda, and Mombasa, Kenya. We predicted the effect of initiating at different immunological thresholds (<200, <350, <500 cells/μL) and increasing access to second-line therapy on the overall and mutation-specific TDR prevalence, as well as infections averted, over 10 years.

Findings

When initiating treatment at CD4 <350 cells per μL we predict 18 and 46 infections averted for each incident case of TDR in Kampala and Mombasa, respectively, and 22 and 32 infections averted when initiating at <500. Between 2012 and 2022, TDR prevalence will increase from 8.3% and 12.3%, to 9.4% and 11.1% when ART is initiated at CD4 <200 cells per μL, to 11.6% and 13.4% when ART is initiated at <350 and to 17.8 % and 18.7% when initiated at <500 in Kampala and Mombasa, respectively. Non-nucleoside reverse transcriptase inhibitor (NNRTI) mutations will continue to dominate the future prevalence of TDR. However, when 80-100% of individuals with virological failure are switched to second-line, TDR is predicted to decline for all immunological thresholds.

Interpretation

The absolute number of incident HIV infections is predicted to be strongly reduced by early ART initiation. This outweighs the risk of the predicted increase in TDR. The effectiveness of first-line NNRTI-based therapy can be preserved by improving switching practices to second-line therapy.

INTRODUCTION

Since 2010, the World Health Organization (WHO) recommends earlier initiation of combination antiretroviral therapy (ART) for HIV-infected persons in resource-limited countries. This guideline change, from initiation at <200 to <350 CD4 cells per µL, has resulted in a substantial increase in the number of people eligible to initiate ART.[1] In addition to the individual clinical benefits,[2] earlier initiation of ART may reduce HIV incidence rates and the concept of treatment as prevention has attracted attention as a means to reduce the global HIV epidemic.[2]

As access to ART is expanded in resource-limited countries, concerns surrounding increasing numbers of patient failing treatment and the consequent emergence of drug resistant viruses will become increasingly important. Resistant virus selected for during treatment may subsequently be transmitted to newly infected individuals, undermining the effectiveness of currently recommended or available first-line ART.[3] A recent comprehensive assessment of transmitted drug resistance (TDR) reported a significant rise in prevalence of predominantly non-nucleoside reverse transcriptase inhibitor (NNRTI)-associated resistance since ART rollout in east and southern Africa.[4] The highest TDR levels (9-13%) have been detected in East Africa.[5-6] As NNRTIs are the cornerstone of standard first-line ART in sub-Saharan Africa, reduced susceptibility to this drug class is especially worrisome in view of the limited availability of alternative first-line drug options.

Mathematical modeling is an important tool to inform policy makers about the potential consequences in terms of HIV drug resistance as a result of increased ART coverage in sub-Saharan Africa. Models of HIV transmission have been used to predict emergence of TDR,[7-10] but these models have not examined the impact of earlier treatment initiation. In this study we used a compartmental mathematical model to predict whether initiation of ART at different immunological thresholds and the availability of second-line ART have an effect on transmission of drug-class specific resistance in East Africa. Specifically, we examined whether the number of new HIV infections averted by early ART initiation offsets a potential rise in TDR.

METHODS

Study design and population

To predict time trends of TDR our model included resistance data from PharmAccess African Studies to Evaluate Resistance (PASER). This comprised two distinct observational studies on transmitted (PASER-Surveillance) and acquired (PASER-Monitoring) drug

resistance conducted in Kampala, Uganda and Mombasa, Kenya (Table 1). PASER-Monitoring used a prospective cohort method with a follow-up of 24 months that assessed HIV drug resistance in individuals initiating first-line ART in 2007-2008.[11] Viral load and drug resistance testing were not used to inform clinical decisions. PASER-Surveillance comprised two cross-sectional surveys among newly HIV-1 diagnosed, antiretroviral-naïve individuals attending voluntary counseling and testing sites in Kampala and Mombasa in 2009-2010.[5-6] Specimens collected in the PASER studies were genotyped in reference laboratories in the *pol* gene in two Uganda, which participated in quality assessment schemes for genotypic drug resistance testing.

Model and calibration

A compartmental deterministic mathematical model was constructed which stratified disease progression into an acute stage, three chronic stages, and two AIDS stages (Figure 1). Three chronic stages were included to indicate previous (ART initiation at CD4 <200 cells per μL[12]),[1] current (CD4 <350 cells per μL),[1] and potential future treatment guidelines (CD4 <500 cells per μL).[13] Infectivity varied by stage of infection.[14-15] Other key model parameters are summarized in Table 2. TDR was defined as the number of individuals infected with drug resistant HIV over total number of HIV infected treatment-naïve individuals.

The model identified four sexual activity groups ranging in the number of new sexual partners per year.[16] Using Monte Carlo filtering techniques,[17] we parameterized the different sexual activity groups and only accepted the simulations that were associated with distinct HIV prevalence from WHO data[18-19] and TDR prevalence in the two PASER-Surveillance sites. For Kampala, this resulted in 1017 simulations with HIV prevalence between 7.1-8.4% between 2005 and 2009 and TDR prevalence between 7.1-10% in 2009. For Mombasa, this resulted in 1247 simulations with an HIV prevalence of 5.8-8.2% between 2006 and 2010, and TDR prevalence between 11.9-14.9% in 2009.

Data and Additional Parameters

The PASER-Monitoring data from initially ARV-naïve patients were used as parameters in the model regarding regimens used and resistance patterns. In 2008-9, approximately 40% of individuals from PASER-Monitoring in Kampala were receiving tenofovir-containing regimens, and 60% zidovudine-containing regimens, both combined with emtricitabine or lamivudine and efavirenz or nevirapine. In Mombasa, just 1% of individuals were on tenofovir-containing regimens, and all others were on zidovudine or stavudine-containing regimens (Table 1). We assumed that stavudine would be phased out and replaced by zidovudine in Mombasa. We also evaluated the impact of instead replacing stavudine by tenofovir in a sensitivity analysis. Specific drug resistance mutations were assumed to be selected for by tenofovir (i.e. K65R) and zidovudine (i.e.

Table 1. Characteristics of patients included in the PASER studies

	Kampala, Uganda	Mombasa, Kenya
PASER-Surveillance cross-sectional survey among recently infected individuals		
Number of participants	77	81
Year of enrolment	2009-2010	2009-2010
Site Type	Voluntary Counselling and Testing	Voluntary Counselling and Testing
Age, years	22.0 (20.0-23.0)	23.4 (21.6-24.9)
Sex, female	54 (70.1)	71 (87.7)
CD4 cells per µL	417 (318.5-551.5)	400 (239-564)
Viral load, $\log_{10}$ c/ml	4.49 (3.96-5.28)	4.6 (4.2-5.1)
Any DRM	6 (8.6)[a]	9 (13.2)[b]
NRTI mutation	2 (2.9)	1 (1.5)
NNRTI mutation	3 (4.3)	5 (7.4)
PI mutation	1 (1.4)	3 (4.4)
PASER-Monitoring longitudinal study among patients receiving first-line ART		
Number of participants	203	221
Year of enrolment	2007	2007-2008
Site Type	Government HIV clinic	Government general hospital
Age, yrs	36.0 (29.2-40.9)	36.4 (31.2-42.8)
Sex, female	113 (55.7)	131 (59.3)
Initial ART regimens		
Zidovudine-containing	122 (60.1)	171 (77.4)
Tenofovir-containing	81 (39.9)	3 (1.3)
Stavudine-containing	0	47 (21.3)
CD4 count at ART initiation, cells per µL	136 (40-206)	128 (63-197)
Viral load at baseline, $\log_{10}$ c/ml	5.4 (5.0-5.9) $\log_{10}$ c/ml	4.6 (4.1-5.4)
Previous ARV exposure	15 (7.4)	10 (4.5)
VL > 400 cps/ml at 12 months	25 (14.3)[c]	21 (11.6)[d]
Any DRM at 12 months	17 (77.3)[e]	6 (46.2)[f]
NRTI mutation	12 (54.6)	4 (30.8)
NNRTI mutation	14 (63.6)	4 (30.8)
PI mutation	1 (4.5)	1 (7.7)
VL > 400 cps/ml at 24 months	25 (15.5)[g]	20 (13.6)[h]
Any DRM at 24 months	15 (75.0)[i]	12 (70.6)[j]
NRTI mutation	11 (55.0)	10 (58.8)
NNRTI mutation	14 (70.0)	12 (70.6)
PI mutation	1 (5.0)	0

Data are presented as n (%) or median (IQR). [a]For n=70 with available genotype; [b]For n=68 with available genotype; [c]For n=175 retained in care; [d]For n=181 retained in care; [e]For n=22 with available genotype; [f]For n=13 with available genotype; [g]For n=161 retained in care; [h]For n=147 retained in care; [i]For n= 20 with available genotype; [j]For n=17 with available genotype. PASER, PharmAccess African Studies to Evaluate Resistance; ART, antiretroviral therapy; ARV, antiretroviral; DRM, drug resistance mutations; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

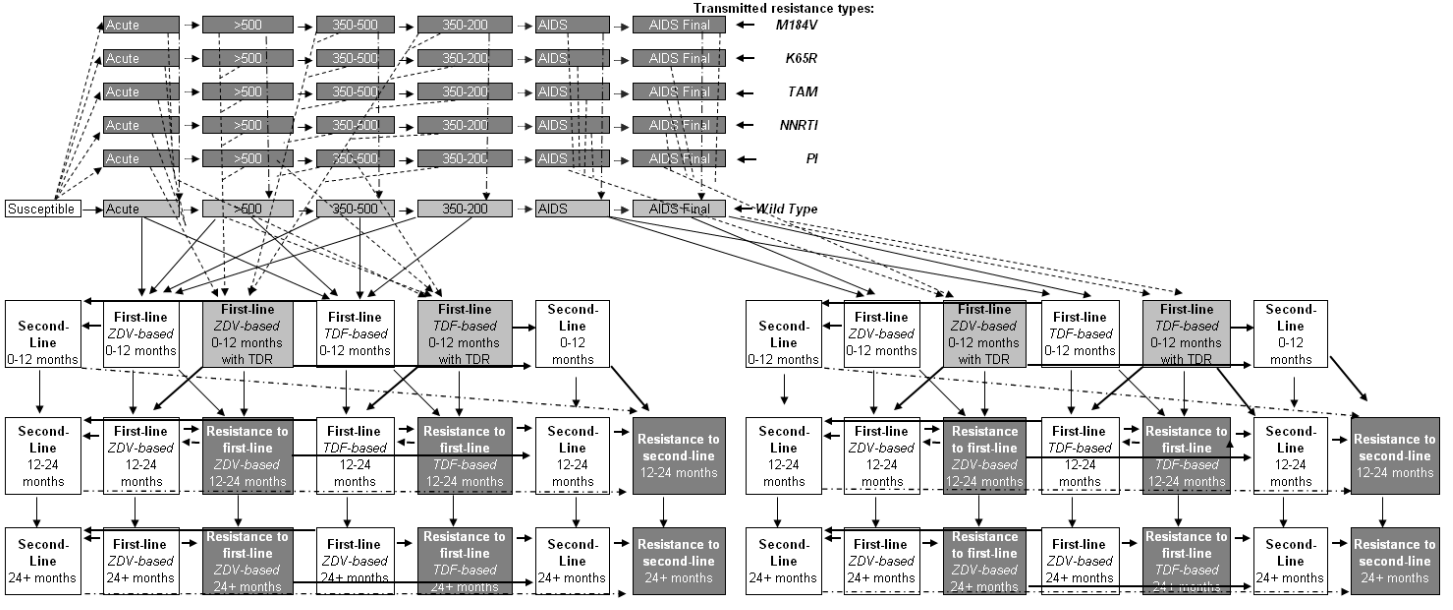


Figure 1. Structure of the compartmental deterministic model. Without treatment, infected patients progress through six stages: the acute stage, the chronic stage (divided into CD4 counts of >500, 350-500, and 200-350 cells per µL), an AIDS stage in which patients have a limited level of sexual activity and the final AIDS stage in which patients have no sexual activity. Individuals in the dark grey boxes are carrying a particular drug resistant virus and can pass on that virus to a susceptible individual. Individuals in the light grey boxes (before treatment) can pass on a wild-type virus to a susceptible individual. Individuals on treatment have a reduced infectiousness and move through three different periods defined by the time since start of antiretroviral therapy and the disease stage in which treatment was started. All boxes have different mortality rates.

Table 2. Additional Model Parameters

Description	Estimate or Range*	Reference
Disease stages duration		25-26
Acute stage	10-16 weeks	
Chronic stage >500 cells per µL	0.87-1 year	
Chronic stage 350-500 cells per µL	2.9-3.1 years	
Chronic stage 200-350 cells per µL	3.6-3.9 years	
AIDS stage**	6-12 months	
Final AIDS stage**	7-13 months	
Infectivity		14-15
Acute stage	27-43 x that of chronic stage	
Chronic stage (all)	10% per year	
AIDS stage**	3-5 x higher than chronic stage	
Final AIDS stage**	0%	
Proportion of people in sexual risk groups		Model Calibration
Highest	1.5-2.5%	
2nd	10-20%	
3rd	20-30%	
Lowest	47.5-68.5%	
Number of partners per year in each sexual risk group		Model Calibration
Highest	9-14	
2nd	1.7-3	
3rd	0.12-0.22	
Lowest	0.04-0.06	
Mortality rates per year		27
Population	0.02	
Chronic HIV stage	0.098	
AIDS stage	0.63	
On treatment during chronic stage, first year	0.02-0.098	
On treatment during chronic stage, 12+ months	0.02-0.05	
On treatment during AIDS stage, first year	0.03-0.3	
On treatment during AIDS stage, 12+ months	0.03-0.06	
HIV Test Rate		
Baseline	10-30%	Model Calibration
Rate of being tested in the acute stage of HIV	Half of the test rate	Assumption***
Rate of being tested in the chronic stage of HIV	test rate	Model Calibration
Rate of being tested in the AIDS stage	test rate + 10%	
Linkage to care from test to treat	75-100%	Model Calibration
Reduction in transmissibility of those patients on treatment	90-100%	2, 28-29
Reduction in transmissibility of those patients on treatment with a transmitted drug resistance virus	80-100%	Assumption

Table 2 (continued)

Description	Estimate or Range*	Reference
Percentage of people that go to second line after continued virological failure Kampala, Uganda, on zidovudine-based regimen on tenofovir-based regimen Mombasa, Kenya, on zidovudine/stavudine-based regimen	33-50% 33-66% 15-30%	PASER-Monitoring, Kampala PASER-Monitoring, Mombasa
Percentage of those who go onto second-line not due to resistance in the first 12 months	1.5-3%	30

*All ranges are uniformly distributed
**Two AIDS stages were included because during the final months before death, patients have limited sexual activity
*** Due to window phase of antibody-based test

thymidine analogue mutations [TAMs]), for lamivudine and emtricitabine (i.e. M184V), and as well as efavirenz and nevirapine (i.e. NNRTI-specific mutations). Individuals were classified as receiving either a zidovudine-containing or tenofovir-containing regimens, and within these regimens, there were different probabilities of acquiring the signature mutations of zidovudine/tenofovir as well as the M184V or NNRTI-specific mutations. The model also included second-line treatment which consisted of a ritonavir-boosted protease inhibitor (PI) in combination with two nucleoside reverse transcriptase inhibitors (NRTIs). Each different regimen (zidovudine-, tenofovir-, or PI-based) was assumed to have a different likelihood of transmitting acquired drug resistant mutations onwards to a susceptible individual.[20] In our model, those with an acquired drug resistant virus could either pass on a NRTI mutation (divided further into a TAM, M184V, or K65R), NNRTI mutation, or PI mutation. A specific fitness cost, estimated by a reduction in replication capacity, was included for each individual mutation.[20] Reversion to wild-type after infection with a drug resistant virus was also considered.

As a baseline scenario, we calculated the TDR prevalence for ART initiation at <200 CD4 cells per µL (including 20% of patients with CD4 200-350 cells per µL). We then predicted the effect on TDR prevalence of ART initiation at CD4 <350 and <500 cells per µL. The total number of people accessing treatment depends on the HIV testing and retention rate, both of which were calibrated in the model. We also investigated the impact of increasing access to second-line therapy. We expected an increased availability of second line regimens and viral load testing in the future. Accordingly, we increased the proportions of people who switch to second-line therapy after continued virological failure in Kampala and Mombasa from 33-66% and 15-30%, respectively, to 80-100%. We then determined the overall and mutation-specific TDR prevalence over 10 years for all immunological ART initiation cut-offs.

In order to investigate whether the prevention of new infections by earlier initiation of ART offsets rising TDR, we calculated the total number of new HIV infections averted for each additional case infected with drug resistant HIV.

RESULTS

Impact of ART on the HIV epidemic

Figure 2A shows the effect of earlier first-line ART initiation on estimated HIV prevalence in Kampala and Mombasa. Although the HIV prevalence remains relatively stable when treatment is initiated at <200 or <350 CD4 cells per µL due to reduced mortality of infected individuals, a decline in HIV prevalence is expected when treatment is initiated at <500 CD4 cells per µL. HIV incidence is expected to drop in both cities when treatment is initiated at <350 and <500 CD4 cells per µL (Figure 2B). The decrease in HIV incidence is also reflected in the proportion of infections that can be averted at particular immunological

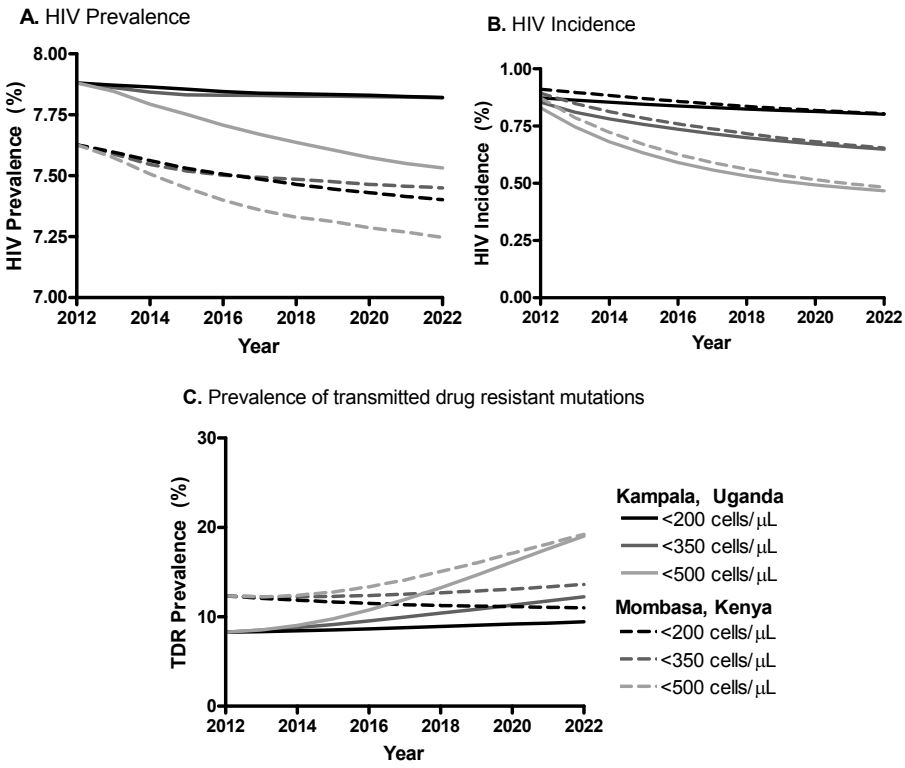


Figure 2. HIV Prevalence, incidence, and overall transmitted drug resistance prevalence from 2012-2022 when initiating treatment at CD4<200 cells per µL, <350 cells per µL, and <500 cells per µL in Kampala, Uganda, and Mombasa, Kenya.

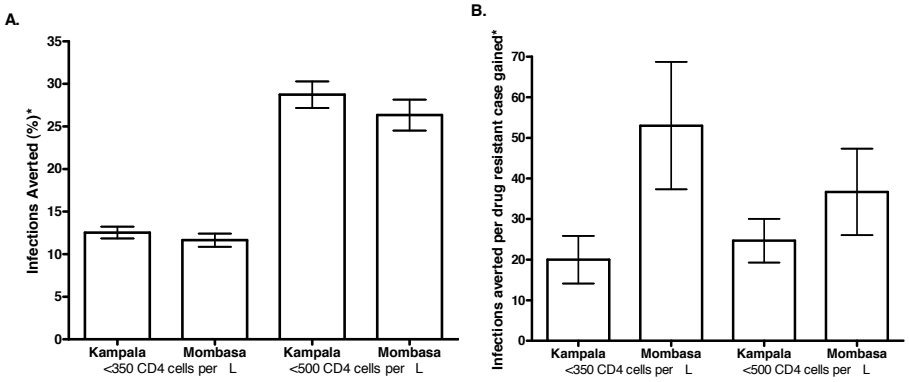


Figure 3. (A) Infections averted (%), in Kampala, Uganda, and Mombasa, Kenya compared to initiating treatment at CD4 <200 cells per µL. (B) Infections averted per additional drug resistant case in Kampala, Uganda, and Mombasa, Kenya compared to initiating treatment at CD4 <200 cells per µL.
*Error bars represent the inter-quartile range.

thresholds of ART initiation. Compared to initiating ART at CD4 <200 cells per µL, initiating ART at CD4 <350 cells per µL averts 12.6% (Inter-quartile range (IQR) 11.3%-13.7%) of infections over 10 years in Kampala and averts 11.6% (IQR 10.3%-13.0%) of infections in Mombasa. Initiating ART at CD4 <500 cells per µL averts 28.8% (IQR 26.0%-31.4%) and 26.3% (IQR 23.2%-29.5%) in Kampala and Mombasa, respectively (Figure 3A).

Prevention of new infections and increase of TDR

When treatment is initiated at CD4 <350 cells per µL, 18 (IQR 11-31) infections in Kampala and 46 (30-83) infections in Mombasa will be averted for every additional case infected with drug resistant virus. Similarly, when treatment is initiated at CD4 <500 cells per µL, the estimated number of infections averted per additional case of TDR will be 22 (17-35) in Kampala and 32 (IQR 21-57) in Mombasa (Figure 3B). The larger number of infections averted in Mombasa as compared to Kampala is in line with the smaller TDR increase predicted in Mombasa.

Evolution of overall TDR prevalence

Figure 2C shows that expanding access to ART by initiating treatment at higher CD4-counts is expected to increase TDR prevalence in both Kampala and Mombasa. Between 2012 and 2022, the estimated TDR prevalence in Kampala increases from 8.3% (IQR 7.7%-9.0%) to 9.4% (IQR 8.4%-10.5%), 12.2% (IQR 10.9%-13.8%) and to 19.0 % (IQR 16.5%-21.8%) when initiating ART at CD4<200, <350 or <500 cells per µL, respectively. During the same period, the estimated TDR prevalence in Mombasa remains 12.3% (IQR 11.7%-13.1%) when starting ART at CD4 <200 cells per µL, but increases to 13.6% (IQR 12.5%-14.9%) when starting at CD4 <350 cells per µL and to 19.2% (IQR 17.1%-21.5%) when starting at CD4 <500 cells per µL.

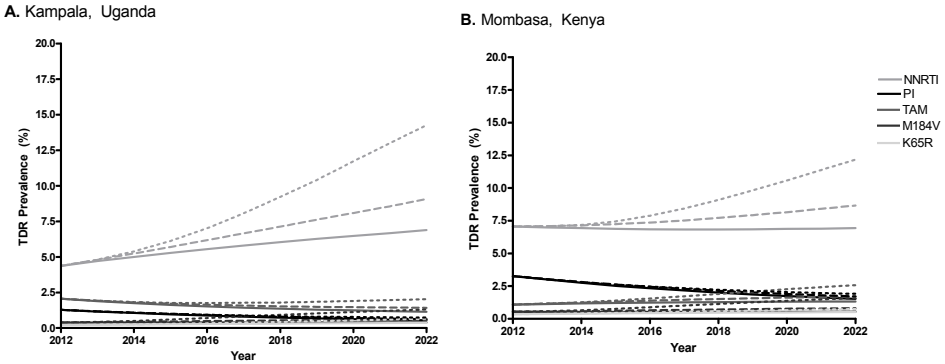


Figure 4. Transmitted drug resistant mutation prevalence by mutation, from 2012-2022 when starting treatment at CD4<200 cells per µL, <350 cells per µL, and <500 cells per µL in Kampala, Uganda, and Mombasa, Kenya. Solid line: treatment initiated at CD4 <200 cells/µL. Dashed line: treatment initiated at **CD4 <350** cells/µL. Dotted line: treatment initiated at CD4 <500 cells/µL.

Drug Resistance by drug class and mutation

In both settings, current TDR is predominantly characterized by resistance to NNRTIs. According to our modeling results, NNRTI mutations are predicted to continue to dominate the future prevalence of TDR (Figure 4A and B). In Kampala, the prevalence of transmitted NNRTI resistance is estimated to rise over the next ten years from 4.4% (IQR 3.8%-4.9%) to 6.9% (IQR 6.0%-7.9%) when initiating at CD4 <200 cells per µL. An increase to 9.1% (IQR 7.8%-10.5%) when initiating treatment at CD4 <350 cells per µL is predicted, and to 14.3% (IQR 11.9%-16.6%) when initiating at CD4 <500 cells per µL. In Mombasa, NNRTI resistance is estimated to remain stable (7.1%; IQR 6.3%-7.7% in 2012 to 6.9%; IQR 6.0%-7.9% in 2022) when initiating ART at CD4 <200 cells per µL, but to increase to 8.7% (IQR 7.6%-9.7%) when initiating at a CD4 count of <350 and to 12.2% (IQR 10.9%-13.7%) when starting at <500. With respect to the NRTI class, in Kampala, estimated prevalence of TAMs decrease between 2012 and 2022, regardless of the immunological threshold used. In contrast, the TAM prevalence in Mombasa is estimated to slightly increase over the same period. A sensitivity analysis in which stavudine was replaced by tenofovir instead of zidovudine yielded similar results (data not shown). Transmitted M184V increases in both Kampala and Mombasa when treatment is initiated at CD4 <500 cells per µL, although the prevalence was predicted to remain <2% in both areas. In both cities, PI resistance decreases over time, irrespective of immunological threshold used to initiate therapy. Transmitted K65R will increase slightly at all immunological thresholds but will remain <1% between 2012 and 2022 in both settings.

Increasing access to second-line

If access to virological monitoring and second-line treatment increases in parallel to the further scale-up of first-line ART, TDR is not expected to increase at any of the immuno-

logical thresholds used for ART initiation. In the scenario where 80-100% of individuals with continued virological failure are appropriately switched to second-line boosted PI therapy, the level of TDR is expected to decline in both locations at all immunological thresholds to below the 2012 TDR level. Increasing access to boosted PIs will either reduce or stabilize TDR for all drug classes (Figure 5A-D).

DISCUSSION

We have modeled the impact of ART initiation at different immunological thresholds on the prevalence of TDR in two East African settings over the next ten years. This is the first model to show that the benefits of early treatment initiation outweigh the risk of increased TDR. We predict that the number of infections that will be averted by earlier ART initiation will far exceed the number of infections with a drug resistant virus.

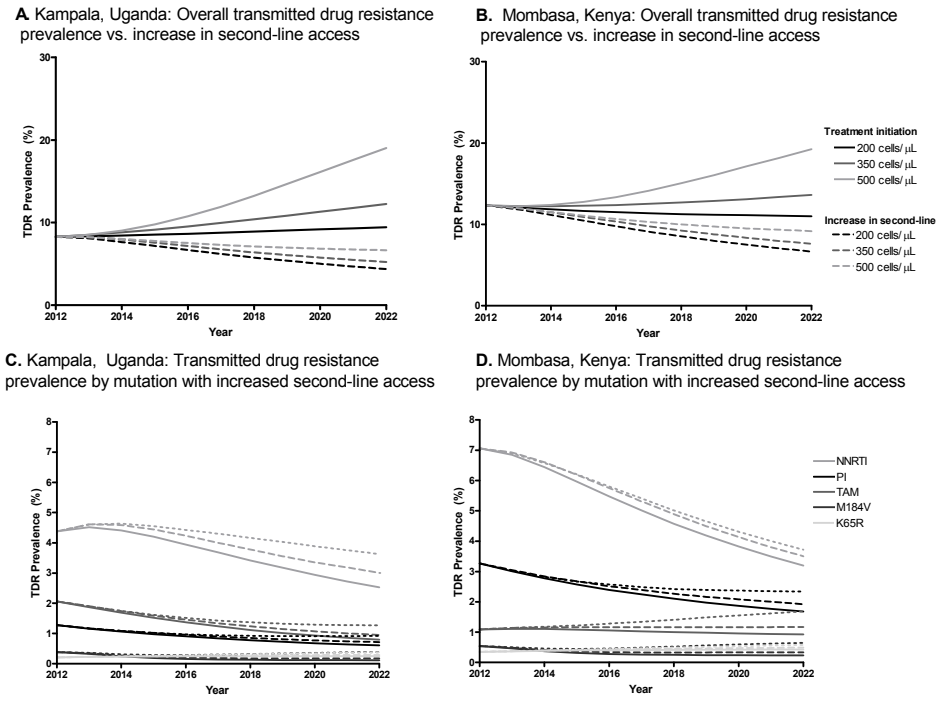


Figure 5. Increasing access to second-line treatment for those with continued virological failure to 80-100% from 2012-2022 when starting treatment at CD4<200 cells per µL, <350 cells per µL, and <500 cells per µL in Kampala, Uganda, and Mombasa, Kenya. Solid line: treatment initiated at CD4 <200 cells/µL. Dashed line: treatment initiated at CD4 <350 cells/µL. Dotted line: treatment initiated at CD4 <500 cells/µL.

When the current WHO treatment guidelines of ART initiation at CD4<350 cells per µL are implemented, TDR prevalence is expected to increase slightly. Expanding treatment by initiating ART at CD4 <500 cells per µL will lead to an increasing TDR prevalence. TDR mutations associated with the NNRTI drug class, the cornerstone of current first-line regimens,[21] are expected to drive the TDR rise. Importantly, if switches from first- to second-line occur for all patients necessitating a switch, then the overall TDR prevalence, including NNRTI resistance, will decrease in the next ten years. This implies that wider access to virological monitoring and boosted PIs for second-line therapy will preserve the effectiveness of NNRTI-based first-line treatment in all scenarios.

Current and predicted TDR is predominantly due to NNRTI resistance. This finding corroborates a recent meta-analysis of TDR which estimated an increase of predominantly NNRTI-related resistance of 29% per year in East Africa.[4] This can be explained by the low genetic barrier of NNRTIs for HIV drug resistance as only a single amino acid substitution is sufficient for high level resistance.[22] In addition, transmitted NNRTI-associated mutations persist for a prolonged period of time.[23] Transmission of NNRTI resistance can have important clinical ramifications as their presence is associated with an increased risk of virological failure of standard first-line treatment and for further selection of drug resistance after treatment initiation.[3] Our modeling study suggests that this can be prevented by increasing access to boosted PIs in second-line ART. Timely switches to second-line regimens are only possibly when routine virological monitoring, i.e. at 6- or 12-monthly intervals, is implemented. In agreement, a recent model of HIV transmission predicted that routine virological monitoring in patients on ART can reduce TDR.[7] For this purpose, cheap point-of-care viral load assays should be developed.[4, 7]

Our mathematical model has several strengths. To our knowledge, our model is the first to examine the impact of initiating ART at different immunological thresholds, including at CD4 <500 cells per µL, on the prevalence of TDR in sub-Saharan Africa. This is particularly relevant in light of increased interest for early initiation of ART as a means to prevent new infections. We have demonstrated that the number of new infections prevented by earlier ART initiation far outweighs the expected number of infections with drug resistant virus. Second, our analysis predicts future levels of HIV drug resistance in sub-Saharan Africa in terms of the presence of specific mutations to particular drugs, accounting for variation in transmissibility between individual mutations. A small number of mathematical HIV transmission models have examined the impact of antiretroviral drugs on transmitted drug resistance in sub-Saharan Africa.[7-10] Almost all previous models used overall TDR rates to describe HIV drug resistance.[8-10] One model used a classification of HIV drug resistance similar to ours, but only reported overall TDR.[7] Lastly, this model combines data on transmitted and acquired HIV drug resistance from the

same geographic areas and time period, collected within the same research project. This is important as resistance acquired during treatment constitutes the pool of variants that can be transmitted within a population. The TDR predictions were largely similar for the two distinct geographic settings even though these two settings have a different history of antiretroviral roll-out. In Uganda, antiretroviral drugs became available at least five years ahead of neighboring countries, including limited-scale distribution of mono and dual NRTI-based therapies.[24] This may account for the higher initial rate of TAMs observed in Kampala, but our analysis shows that it is unlikely to impact future rates of TDR.

This study has some potential limitations. First, the data on acquired resistance do not exceed 24 months of follow-up. Data on HIV drug resistance beyond 24 months of ART in resource-limited settings is scarce. Nonetheless, the PASER-Monitoring study provides the most accurate empirical data on acquired resistance patterns currently available in Africa. Second, we did not incorporate the type of ART monitoring to guide switching, i.e. clinical, immunological or virological, as a variable in our model. Instead, based on PASER-Monitoring data we noted that in Kampala 33-66% and in Mombasa 15-30% of patients with virological failure were appropriately switched to second-line. Third, baseline HIV test rates were assumed to be 10-30% of the populations. Increasing HIV testing uptake is likely to lead to greater numbers of people initiating ART at higher CD4 counts, although this poses logistical challenges for implementation. Fourth, we assumed that drug regimen use would remain constant for the next ten years, as it is difficult to make predictions about future drug substitutions. We did, however, account for the fact that stavudine is likely to be phased out. We assumed that stavudine would be replaced by zidovudine in Mombasa, or instead by tenofovir in a sensitivity analysis, with comparable results.

In conclusion, earlier ART initiation will lead to increased TDR, but this is not expected to offset the preventative benefits in controlling the HIV epidemic. Transmitted NNRTI resistance can potentially have a profound impact on the effectiveness of first-line treatment. Importantly, we have demonstrated that further increase of NNRTI resistance can be avoided by increasing access to second-line boosted PI regimens. Therefore, as ART is scaled-up, efforts should be made to make virological monitoring and effective second-line therapy available. Transmitted drug resistance should not be a reason to withhold early initiation of ART and the use of treatment as prevention in sub-Saharan Africa as the benefits of antiretroviral drugs are predicted to far outweigh the risk of increased transmitted resistance.

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