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Optimizing HIV Drug Resistance Testing Laboratory Networks in Kenya: Insights from Systems Engineering Modeling

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Title: Optimizing HIV Drug Resistance Testing Laboratory Networks in Kenya: Insights from Systems Engineering Modeling

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ABSTRACT

Background: HIV drug resistance (DR) is a growing threat to the durability of current and future HIV treatment success. DR testing (DRT) technologies are very expensive and specialized, relying on centralized laboratories in most low- and middle-income countries (LMIC). Modelling for laboratory network with point-of-care (POC) DRT assays to minimize turnaround time (TAT), is urgently needed to meet the growing demand.

Methods: We developed a model with user-friendly interface using integer programming and queueing theory to improve the DRT system in Kisumu County, Kenya. We estimated DRT demand based on both current and idealized scenarios and evaluated a centralized-laboratory-only network and an optimized POC DRT network. A one-way sensitivity analysis of key user inputs was conducted.

Results: In a centralized-laboratory-only network, the mean TAT ranged from 8.52 to 8.55 working days, and the system could not handle a demand proportion exceeding 1.6%. In contrast, the mean TAT for POC DRT network ranged from 1.13 to 2.11 working days, with demand proportion up to 4.8%. Sensitivity analyses showed that expanding DRT hubs reduces mean TAT substantially while increasing the processing rate at national labs had minimal effect. For instance, doubling the current service rate at national labs reduced the mean TAT by only 0.0% to 1.9% in various tested scenarios, whereas doubling the current service rate at DRT hubs reduced the mean TAT by 37.5% to 49.8%. In addition, faster batching modes and transportation were important factors influencing the mean TAT.

Conclusions: Our model offers decision-makers an informed framework for improving the DRT system using POC in Kenya. POC DRT networks substantially reduce mean TAT and can handle a higher demand proportion than a centralized laboratory-only network, especially for the children and pregnant women living with HIV, where there is an immediate push to use DRT results for patient case management.

KEY MESSAGES:

What is already known on this topic – Little data exists to help optimize HIV drug resistance (DR) laboratory networks in low- and middle-income countries (LMIC). Previous research has highlighted the benefits of POC testing, including increased patient satisfaction, improved adherence to treatment plans, and reduced healthcare costs, in early infant diagnosis and viral load testing in HIV. However, less is known about the role of POC HIV DR testing (DRT) in optimizing laboratory networks.

What this study adds – This study introduces a novel model, utilizing integer programming and queueing theory, for optimizing the laboratory network for the DRT system in Kisumu County, Kenya. The model incorporates a user-friendly interface and evaluates the DRT demand under different scenarios. It compares the performance of the current centralized-laboratory-only network with an optimized network that includes POC DRT. The sensitivity analyses provide valuable insights on key parameters of the optimized DRT network.

How this study might affect research, practice, or policy – The findings of this study can guide decision makers to prioritize the introduction and placement of POC DRT machines, and explore parameters, such as improved batching frequency and increased service rate, to improve their local DRT networks. The tool we developed can also help decision makers assign the optimal referral network fixing the known parameters.

1.0 INTRODUCTION

HIV drug resistance (DR) is a growing threat to the durability of current and future HIV treatment success. The World Health Organization's (WHO) most recent HIV DR report in 2021 notes high concern regarding increasing pre-treatment and acquired DR, especially among children and adolescents living with HIV (CALWH).[1–3] Three countries, Lesotho, Uganda, and Zambia, who conducted systematic HIV DR surveillance among CALWH with viral failure (VF) demonstrated high rates of nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) (50-80%) and non-NRTI (NNRTI) (84-97%) DR. Additionally, accumulation of new DR with continued VF has been documented in both adults and children, further limiting usable ART options.[3,4]

However, DR testing (DRT) technologies are very expensive and specialized, which render them a limited resource.[5,6] Most low- and middle-income countries (LMIC) rely on centralized, highly specialized laboratories and specimen transport networks to conduct DRT for a limited number of patients meeting certain criteria; current low access and high turnaround times, on the order of months, limit even further use of existing DRT options.[7] However, WHO endorses the need for expanded availability of DRT, including point-of-care (POC) options, and acknowledges that use of new HIV treatment options will only expand this need.[8] For instance, while there is marked enthusiasm for dolutegravir-containing treatment options globally,[4,9,10] resistance to dolutegravir is already emerging, stressing the need to monitor dolutegravir DR urgently in LMIC.[11–13] Novel POC, or even near POC, assays are on the horizon to help create greater accessibility to DRT and minimize the return of results challenges often resulting from a centralized testing system.[14] Our group has been involved in the field validation of one such technology called OLA Simple.[15–17] Unpublished Kenya HIV program data suggest better HIV VL results utilization at POC sites than sites supported by centralized laboratory testing systems, which might have implications for POC DRT use as well.

HIV treatment programs in LMIC are expanding VL testing for all people living with HIV (PLWH), therefore, creating more opportunities to detect VF.[18] It is critical to determine how to create decentralized laboratory networks for DRT, possibly including POC DRT assays, to meet the anticipated increase in DRT demand. Different types of decentralized laboratory network models exist in LMIC, including for HIV VL monitoring. Example networks utilize hub-and-spoke or platform sharing.[19–21] Given the even more technical training and expertise needed to conduct HIV DRT compared to HIV VL testing alone, platform sharing is not a likely viable option for DRT shortly. Thus, modeling a network optimization for DRT with a hub-and-spoke model can be useful.

Thus, we aimed to develop a laboratory network optimization model based on systems engineering techniques of queuing in parallel to our VL modeling work for Kisumu County, Kenya.[22] First, we estimated the DRT demand for two scenarios: (1) the current or status-quo scenario of repeated VL testing with adherence counseling that leads to DRT and (2) a more idealized scenario where DRT would be implemented under more liberal guidelines. Second, we created a model for two networks: (1) the status-quo model of utilizing one centralized laboratory at the national level for all DRT testing for Kisumu County and (2) an optimized network that utilized not only the national DRT laboratory but also introduced additional POC DRT hubs. We hypothesized that the second scenario with POC DRT hubs would reduce turn-around time compared to the centralized laboratory model.

2.0 METHODS

2.1 Formative Data Collection

To gather insights into Kenyan policymakers' preferences for model function and decision-making, we conducted formative qualitative research using focus group discussions (FGDs). Details and results can be found in Part 2 of Supplementary materials. We obtained ethical approval from African Medical and Research Foundation (AMREF) and Jaramogi Oginga Odinga Teaching and Referral Hospital (JOOTRH) Institutional Review Boards (IRBs) in Kenya, as well as the University of Washington and the University of Colorado Denver IRBs in the United States, and all study procedures were in line with the Declaration of Helsinki. We identify the research topic as of importance to patients and service users. The policymakers we interviewed help us better understand their needs.

2.2 Current DRT process and selection of POC DRT hubs

In Kisumu County's healthcare system, there are a total of 146 healthcare facilities that collect both HIV VL and DRT samples.[23] After collecting samples from patients, each facility currently sends their samples to one of three central labs (KEMRI CDC HIV/R Laboratory, AMPATH Care Laboratory, and KEMRI/Walter Reed CRC Lab) for HIV VL testing. Once results are returned, patients deemed to not reach viral suppression (defined as VL<200 copies/ml per 2022 Kenya MoH HIV treatment guidelines) undergo discussion with a multidisciplinary team at the facilities,[24] enhanced adherence counseling, including at times directly observed therapy, assessment of and addressing any other causes of viremia, and then repeat VL testing performed three months after the initial viremic episode detection and assurance of enhance adherence efforts.[15] If the patient still has viral non-suppression at repeat VL testing, then providers consult a national-level technical working group to seek advice on DRT. Once that working group reviews the case and approves DRT, the patient is called back to the facility to have another blood sample taken for DRT. This sample is currently sent to one facility, the National Public Health Laboratory (NPHL), to conduct DRT, which it conducts for the entire country for the public sector. While private sector DRT may occur in other facilities, it likely only represents a minority of the DRT occurring in the country. For DRT, the national level laboratory NPHL utilizes Sanger 3730xl for consensus sequencing of samples, which can theoretically process up to 200 samples/day with a more realistic throughput of 100 samples/day based on the available human resource and instrumentation available.

Currently, no POC DRT options are available commercially in Kenya. Our research team has been involved with a field validation of a novel, POC DRT option called OLA Simple.[15–17] From March to June 2021, we piloted this technology at two of the facilities mentioned above, KEMRI CDC HIV/R Laboratory and NPHL. Based on the technical lessons learned from that field validation, we have deemed that the current iteration of the POC DRT platform of OLA Simple still requires a high level of technical expertise and, therefore, can only be implemented at a limited number of sites, unlike many of the POC VL testing platforms. Thus, we have purposefully selected existing highly specialized laboratories for HIV that have pre- and post-PCR rooms, i.e., NPHL, the three existing HIV VL testing labs, and a fourth referral hospital laboratory to the list of potential POC DRT labs, as these facilities can maintain the technical expertise needed to run this assay. Thus, five total DRT laboratories were used to model turnaround time; from here on, we refer to the NPHL as the national laboratory and the other four as POC DRT hubs. We were also restricted to just one POC DRT machine prototype for this modeling exercise. We provide a flowchart of the POC DRT system as Supplementary Figure 1.

2.3 DRT Rate Estimation

Estimating the demand data for DRT has proven challenging due to the structure of publicly accessible routine data and the difficulties associated with using individual-level data, including issues with ID tracking. In addition, missing data and inconsistencies were observed to varying degrees depending on the characteristic.[26] As a result, it is necessary to use estimated proportion of receiving DRT among HIV+ people to approximate the DRT demand.

To incorporate a range of possibilities for the demand of DRT, we considered the following two scenarios based on the overall Kenya MoH HIV treatment guidelines (Figure 1).[24] For Scenario 1, we model the status-quo or current DRT demand based on existing data on high VLs from the available data for Kisumu County from the Kenya MoH HIV VL dashboard.[27] We propose a range of demand values that includes an upper estimate based on the assumption of perfect adherence to the 2022 Kenyan guidelines. This approach is motivated by the observation that the current demand for DRT may underestimate the true need for the service. In the figure, the blocks colored blue represent the chain leading to DRT, with the green blocks showing variable rates. We computed the DRT proportion with combinations of the two varying parameters of (1) percentage of the second VL being conducted (range 25-100%) and (2) the 2nd VL being $\geq$1000 copies/ml (range 25-75%). The estimated proportion of receiving DRT under Scenario 1 ranges from 0.40% to 4.80%. Details of the calculation process can be found in Supplementary Table 2. For Scenario 2, we consider a more idealized case scenario where DRT is recommended earlier in algorithm management, and therefore, chose a lower VL level and earlier step in VL monitoring to conduct DRT, akin to high-income country settings, where DRT is done at first detection of viremia (e.g., DRT requested at 1st VL $\geq$200 copies/ml). This scenario has no variable rates. Of note, while the most recent Kenya MoH HIV treatment guidelines generally recommend using a VL cutoff threshold of $\geq$200 copies/ml as non-suppression, unfortunately, estimates of DRT demand are only available for VL as low as $\underline{4}$00 copies/ml. The estimated proportion of receiving DRT under Scenario 2 is 14.62%.

2.4 Data Acquisition

Our team collected model parameter information through collaboration with Kenyan policymakers and laboratory specialists. **Table 1** lists all model parameters we used in the model, base case values, and their data sources. As a baseline case, we assumed that samples are sent once a week to the national laboratory and daily to other POC DRT hubs by each facility, using motorbikes as the transportation mode, under average road and weather conditions. To test the results under various settings, we conducted one-way sensitivity analyses on several key parameters, including the operational capacity of the national laboratory, the number of machines in hubs, batching mode, and transportation parameters.

2.5 Model: Optimization and Queueing Model

This section outlines the formulation of our optimization model, including decision variables, constraints, and objectives. The primary goal of the model is to improve the total turnaround time of the whole testing system by reorganizing the referral network. Further information about the mathematical expressions used in the model can be found in the Part 3 of Supplementary materials.

The decision variable is a binary referral indicator (i.e., 0 or 1) which connects each facility with testing demand and a potential service site. If their referral indicator is equal to 1, it means the corresponding facility sends their testing samples to that service site. Two constraints are considered for both demand and supply sides. For the demand side, there is one constraint ensuring that each testing demand is met, and the samples are assigned to only one testing facility. For the supply side, the total number of accepted samples for the national laboratory and POC DRT hubs should not exceed its capacity.

The objective of the model is to minimize the overall time it takes to process the DR testing samples across all 146 facilities. This time is made up of three parts: the time it takes for a facility to prepare and send the samples (batching delay), the time it takes for the samples to be transported to the testing site (transportation time), and the time it takes for the samples to be processed at the testing site (processing time).

The processing time in the DRT laboratories was analyzed using queueing models, which are used to represent systems that involve waiting lines. The M/M/s queueing model, one of the most widely studied models, was used to model the arrival and processing of DRT samples at each selected laboratory.[25] Two separate queues were built to reflect the processes: (1) entering samples into the computer system and sample preparation and (2) testing process. The processing time in the system is the sum of these two queueing times.

For practical use, we focused on optimizing two factors - batching delay time and transportation time - in the objective function and add heuristic constraints on utilization rate, avoiding extremely large service time. Details of Excel Decision Support Tool can be found in Part 4 of Supplementary materials.

3.0 RESULTS

The section is organized as follows: Section 3.1 provides a statistical summary of the performance of the system in turnaround time under varying DRT rates; in section 3.2, we visualize the facilities and referral networks on a map; and section 3.3 focuses on the sensitivity analyses for several important operational parameters.

For our following analysis, we compared two different networks: the first network only involved the national laboratory, while the second network introduced four POC DRT laboratories in addition to the national laboratory. We tested both networks in combination with the two different DRT rate estimation scenarios.

3.1 Turnaround Time

We assumed that all samples within a facility would have the same expected turnaround time. By taking the average of the turnaround times per sample from all 146 facilities, we calculated the mean turnaround time. This metric was used to assess the performance of each facility under different conditions. Under the national-laboratory-only network, when DRT rate ranges from 0.4% to 1.2%, the mean turnaround time for all facilities is

about 9 working days, which is consistent with the current observed turnaround time (per unpublished, internal data from NPHL). However, as the DRT rate increases and reaches 1.6%, demand exceeds capacity and waiting times become excessively long, rendering the model infeasible. By contrast, when POC DRT hubs are added to the network, the mean turnaround time reduces to between 1.13 and 2.11 working days, substantially improving system efficiency. The POC DRT hubs network remains feasible until the DRT rate reaches 4.8%, at which point the addition of more POC machines or improvements to the capacity of the national laboratory would be needed to meet the DRT demand. Of note, our results show that as the DRT rate increases, the mean turnaround time exhibits a monotonically increasing trend for both networks. In the POC DRT hubs model, when POC DRT hub capacity is insufficient to meet demand, samples are re-routed to national laboratory. As presented in **Table 2**, the increase in the DRT rate to 2.4% is associated with a marked surge in the standard deviation of turnaround time from 0.05 to 0.87 working days, as well as an escalation in the maximum of turnaround time from 1.71 to 8.56 working days.

3.2 Referral Network Maps

We present a visualization of the referral network, highlighting both national laboratory and POC DRT hubs in Figure 2. The visualizations are organized into different levels of DRT rate (0.4%, 1.2%, 3.6%), each with one plot displaying the complete map encompassing all facilities in Kisumu County. When DRT rate is 3.6%, we provide an additional plot zooming into facilities surrounding Kisumu city to reflect the involvement of the national lab when DRT rate grows. The figure does not contain a panel showing the national-laboratory-only network, since all samples are directed to that laboratory. Typically, facilities forward samples to the POC DRT hub closest to their location, with exceptions arising due to limited capacity at the nearest testing hub. At DRT rates of 0.4% and 1.2%, the referral network is similar, with demand for DRT largely being handled by three POC DRT hubs (KEMRI CDC HIV/R Laboratory, KEMRI/Walter Reed CRC Laboratory, and JOOTRH). At these two levels of DRT rate, the AMPATH Care Laboratory and the national laboratory do not receive any samples from Kisumu County, presumably due to high transportation times. When the DRT rate increases to 3.6%, the referral network expands to incorporate both the AMPATH Care Laboratory and the national laboratory. More specifically, when the DRT demand proportion ranges from 0.4% to 1.6%, no facilities send samples to the national lab. However, when the proportions are 2.4%, 3.2%, and 3.6%, 2, 6, and 9 facilities out of 146, respectively, send samples to the national lab. Those facilities sending their samples to NPHL face substantially longer turnaround times due to the extended transportation and batching times.

3.3 One-Way Sensitivity Analyses

Table 3 outlines the mean turnaround time of all facilities under three different settings for each parameter, as well as their percentage change compared with the baseline results. We ground these changes at a DRT demand rate of 1.2% with the national-laboratory only model, 1.2% with adding four POC DRT hubs model, and 3.6% with the latter model. For quick visualization, a gray scale captures the magnitude of change from baseline.

Batching delay mode had the most substantial impact on the mean turnaround time in the national-laboratory-only network. Specifically, when transitioning from a weekly to a twice-a-week or daily batching delay mode, the mean turnaround time decreased by 34.3% or 80.1%, respectively. In both the national laboratory and POC DRT hubs networks, we observed that adding machines or improving the machine service rate also improved the system's efficiency. For example, the addition of two machines for all existing hubs led to a 40.8% reduction in turnaround time. On the other hand, increasing the operational capacity of national laboratory had a minor impact on the mean turnaround time under all settings, suggesting that expanding the capacity of the national laboratory (e.g., by adding more machines or human resources) would not substantially improve the system's efficiency. In addition, road and weather conditions had negligible effects on the mean turnaround time in all scenarios, while transportation mode had a more substantial impact on the turnaround time, particularly with walking sample delivery—an unlikely scenario—compared to a baseline of motorbike transport (93.5% slower). However, car transport was not meaningfully better (only 2.7% faster) compared to motorbike transport.

4.0 DISCUSSION

Our modeling study, employing systems engineering methodologies, reveals that POC DRT is likely to be required in addition to centralized laboratory testing to realize the demand for DRT in LMICs in the upcoming

years. The existing strategy, in which a solitary national laboratory is responsible for conducting DRT for the entire laboratory network, will rapidly encounter capacity limitations if the DRT demand were to merely triple from 0.4% to 1.2%. The new configuration of a POC DRT network is designed to accommodate up to a ninefold escalation in the baseline rate, from 0.4% to 3.6%. As noted previously, despite marked enthusiasm for dolutegravir-containing regimen use in LMICs, DR will be an enduring concern. DR to dolutegravir is already emerging,[9,28–32] and because it remains unclear what regimens should be utilized in cases of dolutegravir resistance, the use of DRT is only going to increase as surveillance for dolutegravir resistance intensifies in LMICs. Though the maximum potential DRT demand rate (14.6%) modeled in our Scenario 2 is highly improbable to occur in LMICs in the foreseeable future, there is a pressing need for a substantial increase in centralized and POC DRT capacity to cope with the likely upsurge in DRT demand. This increase in capacity will be critical to ensuring that LMICs are able to effectively manage the growing need for HIV DR test especially among the children and pregnant women living with HIV that are more sensitive to return of results.

One of the largest determinants of turnaround time was the batching delay. For instance, increasing the sample transportation frequency from a weekly to a twice-weekly basis could potentially halve the turnaround time. Furthermore, if samples were transported daily, the turnaround time could be halved once again, potentially resulting in more efficient and timely processing of samples. Of course, a trade-off between the cost and labor of frequent shipment against economies of scale of batching need to be considered when determining the batching delay for transport of samples from a spoke to a hub facility. By having closer POC DRT facilities to the spoke facilities than the national laboratory, this issue of batching delay is overcome by a network that includes POC DRT hubs. Since direct data about the impact of POC DRT testing on results utilization has not been studied, parallels with POC VL testing may be useful: although POC VL testing has not necessarily consistently improved viral suppression,[33–35,21] improved turnaround times are highly motivating for providers and patients[36] and results utilization appears to improve as well.[20,34,37]

Another important factor influencing turnaround time is the service rate or operational capacity of POC machines. This expansion of POC machines may lead to very efficient and timely delivery of test results (possibly within one day). However, our study suggests that augmenting the operational capacity of the national laboratory does not have a substantial impact on reducing the mean turnaround time for DRT. This is because facilities continue to experience substantial delays due to the long transport and batching delays involved in sending samples to the national laboratory. Furthermore, since the national laboratory has a limited capacity share reserved for Kisumu County to process samples from other parts of the country, it is fundamentally limited in improving turnaround times for the region. While we did not explicitly model the additive improvements in both increasing the operational capacity at the centralized laboratory and reducing the batching delays, were those factors more easily modifiable for a given national laboratory, it is possible that a national laboratory network could be responsive to the increasing needs of increasing DRT demand over time. Therefore, decision-makers should consider focusing on optimizing POC machine capacity as a potentially more effective approach to improve the overall performance of the DRT network.

Given our findings, we suggest that decision makers should prioritize the introduction of POC DRT machines to meet the current and anticipated demand for DRT in Kisumu County.[7] This would effectively reduce the turnaround time and offer several programmatic advantages. POC has been shown to increase patient satisfaction and adherence,[38] reducing healthcare costs by minimizing multiple clinic visits for result inquiries.[39] Implementing POC DRT hubs addresses access disparities for marginalized communities facing limited investments and ensures proper chain of custody, mitigating specimen rejection and errors in centralized referral networks.[40,41] Onsite POC testing significantly reduces the risk of poor results, enhancing clinical follow-up and confidence in laboratory systems. Additionally, it may be beneficial for decision makers to explore the possibility of improving the frequency of batching samples to the national laboratory and substantially increasing the service rate of POC machines as potential next steps to further enhance the system's performance. Since any of the options should include investing in staff training and development programs, it is important to acknowledge that determining the most efficient use of limited resources to achieve optimal results should be based on a further cost-effectiveness analysis.

Despite unique insights yielded by our model, there are several limitations to this work. First, one of the biggest challenges in selecting POC DRT hubs for DRT is the intrinsic laboratory capacity for that hub to handle the more technical elements related to HIV DR vs. VL testing. This immediately limits the pool of candidate hubs to

a few select facilities already functioning at a relatively high laboratory capacity. Second, the model utilizes VL demand data from 2019, as more recent data may be affected by COVID-19-related VL testing reagent shortages. Third, in this queuing model approach, we consider time delays as one component of costs; however, the models still lack explicit parameterization for monetary costs. Fourth, future models could model clinical decision-making parameters, such as results utilization, to better demonstrate utility of such models. Finally, this model is limited to the service delivery level of Kisumu County and would require expansion for it to be applicable in other counties.

5.0 CONCLUSIONS

In conclusion, our findings provide a valuable framework for improving the current DRT laboratory network system in Kenya, offering decision makers an opportunity to identify ways forward for DRT demand estimation, optimal referral networks and identifying key factors like transportation delays and operational capacity of POC DRT hubs. As the demand for DRT is expected to increase, we recommend the inclusion of POC DRT hubs to handle a larger volume of samples within an acceptable turnaround time.

Table 1: Model parameters, assumptions, and data sources.

Parameter	Base Case Value	Note
HIV VL test demand (per working day)		
HIV VL Testing demand in 146 facilities	Ranges from 0 to 37 (per working day) for different facilities	The quantity of VL samples from each facility is determined through the HIV client volume data from 2019 in Kisumu County's DHIS II. This was necessary because of the COVID-19 pandemic-related interruptions in 2020 and the subsequent nationwide interruptions in VL testing. Details of these estimations can be found in our related work on HIV VL testing.[22] Data Source: http://kmhfl.health.go.ke/ and https://dhis2.org/
DRT rate		
Scenario 1	0.40%~4.80%	Proportion of valid VL tests unsuppressed at VL≥1000 copies/ml threshold * Percentage completing second VL testing * Percentage of second VL≥1000 copies/ml. Details of the data source can be found in Supplementary Table 1, and calculation process with parameters combinations can be found in Supplementary Table 2. Data Source: https://viralload.nascop.org/
Scenario 2	14.62%	Proportion of valid VL tests unsuppressed at VL≥ 200 copies/ml threshold. Of note, we changed the threshold from newly recommended 200 to 400 copies/ml since the data provided does not enumerate values at the 200 copies/ml threshold.[24]
HIV DR test demand (per working day)		
HIV DRT demand in 146 facilities under Scenario 1	Minimum demand is 0; maximum demand ranges from 0 to 2	HIV VL test demand * DRT rate
HIV DRT demand in 146 facilities under Scenario 2	Ranges from 0 to 5	
Transportation		
Distance between all facilities to the national laboratory and POC DRT hubs (km)	0 to 370	We used Google Map API to collect the distance and time data given the name of facilities in Kisumu, Kenya and the locations of the national laboratory and hubs. (https://developers.google.com/maps)
Speed: (km/hour)	5 (walk), 20 (bike), 40 (motorbike)*, 50 (car)	To calculate the transportation time, we provided different types of transportation modes and allowed the user to decide which one to use and estimated the average speed for each transportation mode.
Road condition adjustment coefficient	0.8 (good), 1 (average)*, 1.2 (bad)	We considered different weather and road conditions and allowed users to change these conditions based on their needs. The weather and road conditions are 'good', 'average' or 'bad', and the time needed for transportation could be less given better weather and road conditions.
Weather condition adjustment coefficient	0.8 (good), 1 (average)*, 1.2 (bad)	
Batching delay (min): [frequency with which samples are transported to testing facility (hub or national laboratory)]		
Immediately	0	If the samples are sent immediately once received at the facility due to the scarcity of the demand, we would simply remove the aspect of batching. We assumed that each working day has 7 hours. If the samples are sent daily, the average delay time is half of the working day, which is 3.5 (hours), i.e., 210 minutes. If the samples are sent twice a week, the average delay is a whole day and a working day, which is 24+7 = 31 hours, i.e., 1860 minutes. If the samples are sent only once a week, the average delay is half of 4 whole days and a working day, which is (24*4+7)/2=51.5 hours, i.e., 3090 minutes. As a baseline setting, we assume that the samples are sent daily to DRT hubs and once a week
Daily*	210	
Twice a week	1860	
Once a week**	3090	

		to the national laboratory.
National laboratory (NPHL) queueing parameters		
Entering process		
Mean service rate (test per day)	100	Mean service rate refers to the average number of DR samples received at one central laboratory given current staffing and process steps. Number of servers refers to the number of workers processing the entering of samples. We assume that there are two workers in each central laboratory working on entering the samples into the system.
Number of servers	2	
Machine process		
Mean service rate (test per day)	100	We assume each central laboratory can handle up to 500 samples per week, which in turns to be 100 samples per working day. Estimates based on personal communication with central laboratory managers.
Number of machines at each central lab	1	Estimates based on personal communication with central laboratory managers.
Percentage of DRT samples from Kisumu	7.9%	For 2021, 89 of 1123 DRT samples (7.925%) were from Kisumu County per personal communication with central laboratory managers.
POC DRT hub queueing parameters		
Entering process		
Mean service rate (test per day)	100	Mean service rate refers to the average number of DR samples received at DRT hubs given current staffing and process steps. We assume that there is only one worker in each hub working on entering the samples into the system.
Number of servers	1	
Machine process		
Mean service rate (tests per day)	2	Data source: personal communication with implementing partner director for HIV programs in Kisumu County. OLA DR assay can only do two samples per working day.
Number of servers		
Hub 1: KEMRI CDC	2	Number of servers refers to the number of machines assigned for each hub.
Hub 2: AMPATH	2	
Hub 3: Walter Reed CDC	2	
Hub 4: JOORTH	2	
Percentage of samples from Kisumu		
KEMRI CDC	100%	Given that the POC DRT hubs conduct POC DRT, we assumed all samples coming to these hubs are from facilities within Kisumu County. Of note, because POC DRT will likely be based on point mutation detection, and not full genome sequencing, some of the samples with positive findings on POC DRT may need full genomic sequencing via consensus sequencing at the national, central laboratory. Our DRT demand estimates, and modeling parameters do not account for these few additional DRT samples that may be needed at the national, central laboratory.
AMPATH	100%	
Walter Reed CDC	100%	
JOOTRH	100%	

* represents baseline batching delay mode of sending samples to DRT hubs
** represents baseline batching delay mode of sending samples to national laboratory

Table 2: Statistics summary of mean turnaround time for two networks under various DRT demand proportion.

		National Laboratory Only		National Laboratory & POC DRT hubs	
Scenarios	**DRT Proportion**	**Turnaround time, working days Mean (SD)**	**Turnaround time, working days Min, Max**	**Turnaround time, working days Mean (SD)**	**Turnaround time, working days Min, Max**
Scenario 1	0.4%	8.52 (0.09)	8.33, 8.70	1.13 (0.07)	1.03, 1.30
	0.8%	8.53 (0.09)	8.33, 8.71	1.35 (0.2)	1.04, 1.65
	1.2%	8.55 (0.09)	8.36, 8.73	1.44 (0.15)	1.16, 1.70
	1.6%	Infeasible		1.53 (0.05)	1.46, 1.71
	2.4%	Infeasible		1.69 (0.87)	1.48, 8.56
	3.2%	Infeasible		1.90 (1.49)	1.48, 8.60
	3.6%	Infeasible		2.11 (1.81)	1.49, 8.67
	4.8%	Infeasible		Infeasible	
Scenario 2	14.62%	Infeasible		Infeasible	

Table 3: Results for one-way sensitivity analyses, with mean and standard deviation of turnaround time in working days, and the percentage change from the baseline parameter.

	National-laboratory-only (DRT rate: 1.2%)	National laboratory & POC DRT hubs (DRT rate: 1.2%)	National laboratory & POC DRT hubs (DRT rate: 3.6%)
Capacity Improvement			
Improving operation capacity of the national lab			
current service rate *	8.55 (0.09)	1.44 (0.15)	2.11 (1.81)
1.5 times current service rate	8.52 (0.09), -0.4%	1.44 (0.15), 0.0%	2.07 (1.81), -1.9%
2 times current service rate	8.52 (0.09), -0.4%	1.44 (0.15), 0.0%	2.07 (1.80), -1.9%
Add machines in hubs			
No additional machines *	**	1.44 (0.15)	2.11 (1.81)
Add 1 server for all existing hubs	**	1.23 (0.12), -14.6%	1.47 (0.90), -30.3%
Add 2 servers for all existing hubs	**	1.12 (0.07), -22.2%	1.25 (0.05), -40.8%
Improving operation capacity of hubs			
current service rate*	**	1.44 (0.15)	2.11 (1.81)
2 times current service rate	**	0.90 (0.07), -37.5%	1.06 (0.05), -49.8%
4 times current service rate	**	0.73 (0.06), -49.3%	0.79 (0.08), -62.6%
Batching delay of sending samples to the national lab			
Daily	1.70 (0.09), -80.1%	1.44 (0.15), 0.0%	1.61 (0.11), -23.7%
Twice a week	5.62 (0.09), -34.3%	1.44 (0.15), 0.0%	1.89 (1.06), -10.4%
Once a week*	8.55 (0.09)	1.44 (0.15)	2.11 (1.81)
Transportation parameters			
Road/weather condition			
Good	8.32 (0.07), -2.7%	1.43 (0.15), -0.7%	2.06 (1.76), -2.4%
Average *	8.55 (0.09)	1.44 (0.15)	2.11 (1.81)
Bad	8.78 (0.11), 2.7%	1.46 (0.15), 1.4%	2.13 (1.87), 0.9%
Transportation mode			
Walk	16.54 (0.73), 93.5%	2.04 (0.48), 41.7%	3.38 (3.73), 60.2%
Bike	9.69 (0.18), 13.3%	1.53 (0.17), 6.3%	2.29 (2.08), 8.5%
Motorbike *	8.55 (0.09)	1.44 (0.15)	2.11 (1.81)
Car	8.32 (0.07), -2.7%	1.43 (0.15), -0.7%	2.06 (1.76), -2.4%

* represents baseline parameter settings

The legend of the gray scale plot:

Gray Scale	Scale (working days)
	0~2

	2~4
	4~6
	6~8
	8~10
	≥ 10

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Sex and/or Gender Data Disaggregation
We have not pursued sex and/or gender data disaggregation for the modeling work, as none of the modeling parameters are contingent on sex and/or gender.

Author Reflexivity Statement
Has the research team engaged constructively with the reflexivity statement? [Yes.]
Have the research partners co-developed the research study? [Yes.]
Does the study address priority research questions for the LMIC partner(s)? [Yes.]
Is there a LMIC partner who is the first or last author? If not, what is the explanation? [Yes.]
How have LMIC early career researchers been incorporated as authors? [Yes, one of the first co-authors is a LMIC partner, who was instrumental in conceptualization, data procurement, and decision to submit manuscript. (see more below).]
How are data shared with LMIC partners to address research needs? [The data are from LMIC settings, and the model itself is shared with LMIC partners for decision-making in LMIC settings.]
Is there open access funding to improve publication dissemination? [Yes.]

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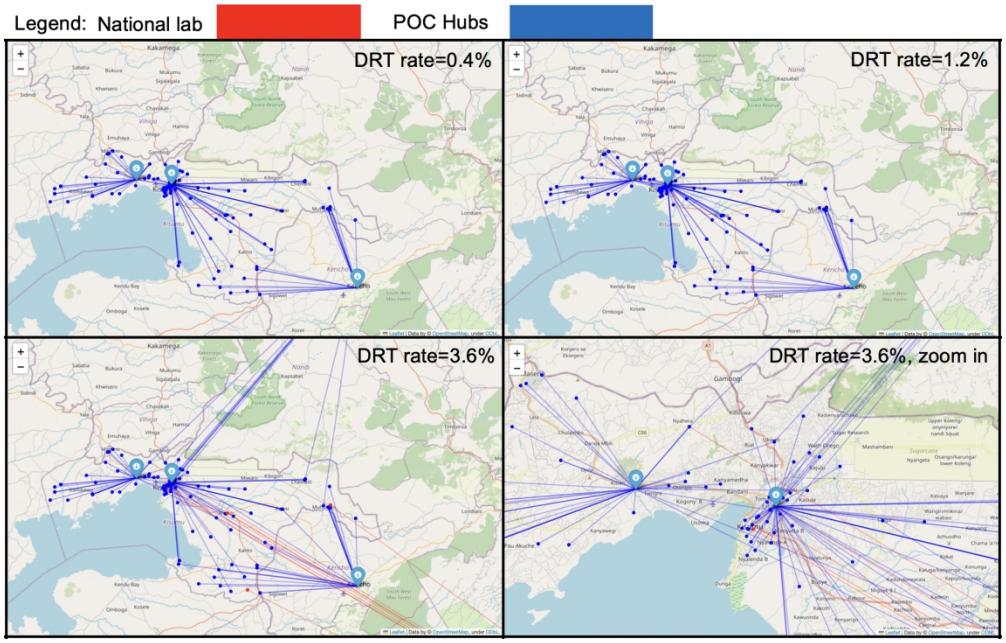
Legend of Figures

Figure 1: Scenario 1 (current DRT based on existing VL data from 2019) and 2 (more idealized DRT) flowchart for DRT demand estimation for Kisumu County, Kenya.

Note:

1. Color Schematic: In both Scenarios 1 and 2, blue colored blocks are utilized to illustrate the trajectory of HIV samples that lead to DRT at the final stage, in accordance with various guidelines. In Scenario 1, green colored blocks are employed to signify the consideration of various rates for conducting a second VL test and the suppressing rate for the second VL.
2. Data source: NASCOP VL database[11]. Details of data used can be found in Supplementary Table 1.

Figure 2: Referral network when POC DRT hubs are included in the testing network, with varying DRT rates and zoom levels. The markers with colors of red and blue correspond to national and four POC DRT hubs, respectively. Additionally, blue dots are used to represent 146 facilities. The network is shown through links between facilities and selected DRT laboratories.



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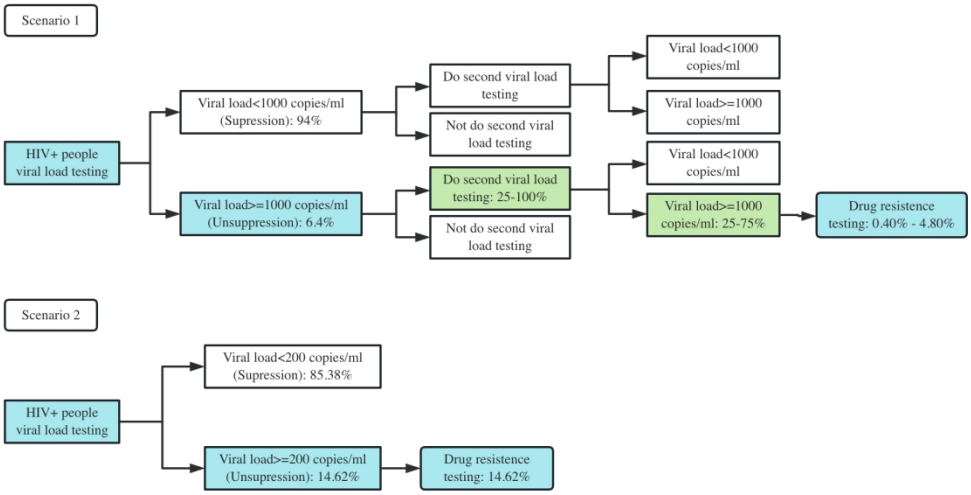

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Supplementary Materials

Part 1: Supplementary Tables and Figures

Supplementary Table 1: Parameters for estimating the DRT rate.

Total VL tests done:	**153,118**		
Routine VL Tests with Valid Outcomes:	143,323	Proportion of Routine VL Tests with Valid Outcomes:	93.60%
Viral Load ≥ 1000 copies/ml:	9,168	Proportion of Tests with Viral Load ≥ 1000 copies/ml:	6.40%
Viral Load < 1000 copies/ml:	134,155	Proportion of Tests with Viral Load < 1000 copies/ml:	93.60%
Viral Load < 400 copies/ml:	122,364	Proportion of Tests with Viral Load < 400 copies/ml:	85.38%
Viral Load 401 - 999 copies/ml:	11,791	Proportion of Tests with Viral Load 401 - 999 copies/ml:	8.23%
Confirmatory Repeat Tests:	8,042	Proportion of Confirmatory Repeat Tests:	5.25%
Viral Load ≥ 1000 copies/ml:	2,309	Proportion of Tests with Viral Load ≥ 1000 copies/ml:	28.71%
Viral Load < 1000 copies/ml:	5,733	Proportion of Tests with Viral Load < 1000 copies/ml:	71.29%
Baseline VLs:	1,753	Proportion of Baseline VLs:	1.14%
Viral Load ≥ 1000 copies/ml:	128	Proportion of Tests with Viral Load ≥ 1000 copies/ml:	7.30%
Viral Load < 1000 copies/ml:	1,625	Proportion of Tests with Viral Load < 1000 copies/ml:	92.70%

Data Source: https://viralload.nascop.org/.

Supplementary Table 2: DRT demand estimation with combinations of percentage of doing second VL testing and percentage of second VL ≥1000 copies/ml.

Proportion of patients receiving DRT	**Percentage of second VL≥1000 copies/ml**		
Percentage completing second VL testing	25%	50%	75%
25%	0.40%	0.80%	1.20%
50%	0.80%	1.60%	2.40%
75%	1.20%	2.40%	3.60%
100%	1.60%	3.20%	4.80%

Note: Proportion of patients receiving DRT = Proportion of valid VL tests unsuppressed at VL≥1000 copies/ml threshold * Percentage completing second VL testing * Percentage of second VL≥1000 copies/ml.

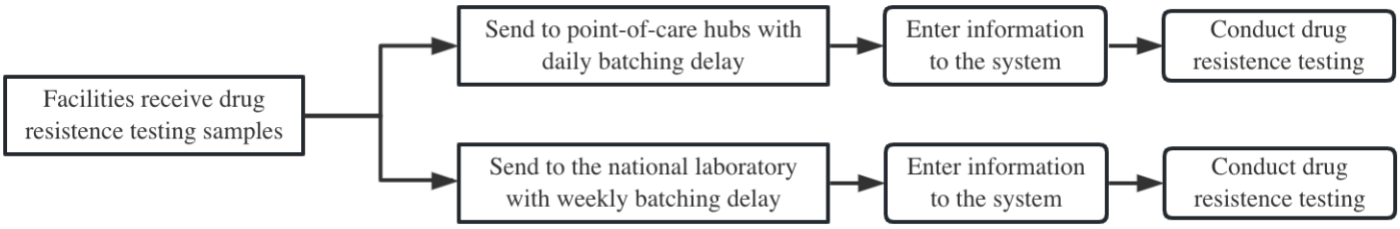
Supplementary Table 3: Demographics of FGD participants (Number of participants: 12).

Characteristic	**Median (IQR) or n (%)**
Age	43 (37.5, 45)
Workstation	
County MOH	11 (92%)
Implementing partner	1 (8%)
Male	8 (67%)
Highest level of education	
Bachelor's degree	6 (50%)
Master's Degree	6 (50%)
Years of education completed	20 (19, 22)
Years working with HIV treatment monitoring	10 (9,13)
Activities related to HIV treatment monitoring currently involved in:	
Managing clinical teams that order or utilize drug resistance results for patient management	11 (92%)

Managing clinical teams that order or utilize viral load results for patient management	9 (75%)
Coordinating logistical issues for HIV laboratory tests	3 (25%)
Regulatory, validation, or verification of HIV-related machines or procedures	3 (25%)
Determining budgets	2 (17%)
Ordering and interpreting viral load for patients	1 (8%)
Ordering and interpreting drug resistance tests for patients	1 (8%)
Other coordination	1 (8%)

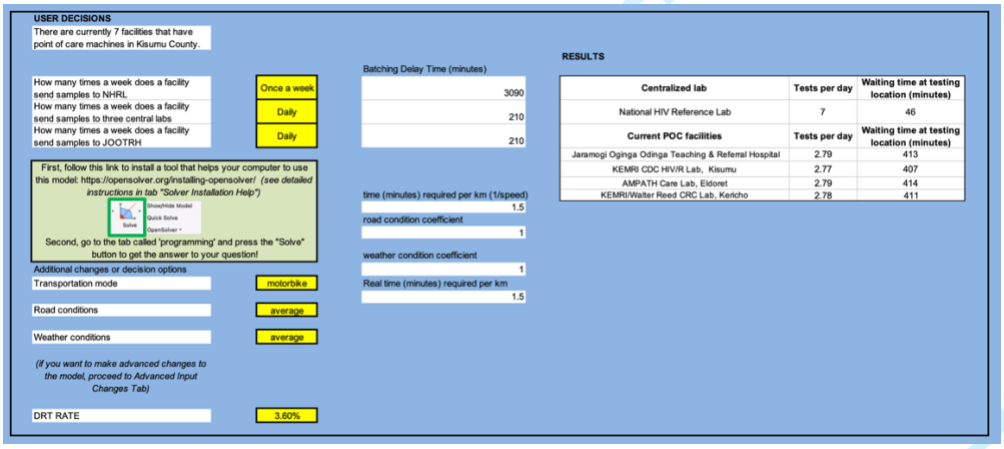
Note: This demographics table is also in the VL paper (Wang & Wagner, Under Review).[22]

Supplementary Figure 1: A flowchart for the working process of the system.



Supplementary Figure 2: Layout of Excel tool: Panel A is the tab "Basic Inputs & Model Outputs" which shows basic parameter inputs and results output and Panel B is the tab "Referral Network" where users can find detailed information for each individual facility.

Panel A:



Panel B:

	MFL Code	Sub County	Facility Name	Total HIV test per day (7 hours)	Hub number or Central labs to go	Expected number of samples at testing location every day	Transportation Time (minutes)	Frequency at which facilities send samples for testing (daily, once a week, twice a week) (minutes)	Expected waiting time at testing location (working days)	Expected waiting time at testing location (minutes)	Total Turnaround Time (minutes)	Total turnaround time (working days)
1	13939	Kisumu Central Sub County	Jaramogi Oginga Odinga Teaching & Referral Ho	33	National HIV Reference Lab	9.8	496.5	3090	0.109	45.9	3632.4	8.6
2	20700	Kisumu Central Sub County	Keeping alive Society Hope	0	Jaramogi Oginga Odinga Teaching & Referral	2.7	4.7	210	0.983	412.7	627.4	1.5
3	24200	Kisumu Central Sub County	LVCT Health Manyatta Dice	0	Jaramogi Oginga Odinga Teaching & Referral	2.7	3.0	210	0.983	412.7	625.7	1.5
4	13856	Kisumu Central Sub County	Nightingale Medical Centre	2	Jaramogi Oginga Odinga Teaching & Referral	2.7	2.3	210	0.983	412.7	625.0	1.5
5	20956	Kisumu Central Sub County	AAR Health care-Kisumu	0	Jaramogi Oginga Odinga Teaching & Referral	2.7	4.5	210	0.983	412.7	627.2	1.5
6	13465	Kisumu Central Sub County	Aga Khan Hospital (Kisumu)	0	Jaramogi Oginga Odinga Teaching & Referral	2.7	3.2	210	0.983	412.7		
7	13704	Kisumu Central Sub County	Kisumu County Hospital	32	National HIV Reference Lab	9.8	495.0	3090	0.109	45.9	3630.9	8.6
8	19869	Kisumu Central Sub County	Kisumu Police Line Dispensary	0	Jaramogi Oginga Odinga Teaching & Referral	2.7	6.2	210	0.983	412.7		
9	16662	Kisumu Central Sub County	Liverpool VCT (Kisumu East)	16	National HIV Reference Lab	9.8	495.0	3090	0.109	45.9	3630.9	8.6
10	27025	Kisumu Central Sub County	Maygo Railways	0	Jaramogi Oginga Odinga Teaching & Referral	2.7	2.1	210	0.983	412.7		
11	13808	Kisumu Central Sub County	Milimani Hospital	0	Jaramogi Oginga Odinga Teaching & Referral	2.7	5.4	210	0.983	412.7		
12	14027	Kisumu Central Sub County	Railways Dispensary (Kisumu)	7	KEMRI CDC HIV/R Lab, Kisumu	2.7	17.7	210	0.970	407.4	635.1	1.5
13	20523	Kisumu Central Sub County	Tumaini Dice Dispensary (Kisumu)	2	Jaramogi Oginga Odinga Teaching & Referral	2.7	6.2	210	0.983	412.7	628.9	1.5
14	13807	Kisumu Central Sub County	Migosi Sub County Hospital	8	AMPATH Care Lab, Eldoret	2.8	159.0	210	0.986	414.2	783.2	1.9
15	13887	Kisumu Central Sub County	Nyalenda Health Centre	2	Jaramogi Oginga Odinga Teaching & Referral	2.7	8.6	210	0.983	412.7	631.3	1.5
16	14012	Kisumu Central Sub County	Pand Piet Community Dispensary	13	AMPATH Care Lab, Eldoret	2.8	168.0	210	0.986	414.2	792.2	1.9
17	16682	Kisumu Central Sub County	St Jones and Ring Road Health Clinic	0	Jaramogi Oginga Odinga Teaching & Referral	2.7	1.5	210	0.983	412.7		
18	13464	Kisumu Central Sub County	Administration Police Dispensary (Kisumu)	2	Jaramogi Oginga Odinga Teaching & Referral	2.7	2.9	210	0.983	412.7	625.6	1.5
19	21220	Kisumu Central Sub County	Anza Mapema Clinic	0	Jaramogi Oginga Odinga Teaching & Referral	2.7	1.7	210	0.983	412.7		
20	20123	Kisumu Central Sub County	Avenue Hospital Kisumu	0	Jaramogi Oginga Odinga Teaching & Referral	2.7	3.9	210	0.983	412.7		
21	17554	Kisumu Central Sub County	K-Met Corkran Medical Clinic	0	Jaramogi Oginga Odinga Teaching & Referral	2.7	2.4	210	0.983	412.7	625.1	1.5
22	20836	Kisumu Central Sub County	St Monica Hospital (Town Clinic)	5	KEMRI CDC HIV/R Lab, Kisumu	2.7	21.8	210	0.970	407.4	639.2	1.5
23	13736	Kisumu Central Sub County	Lumumba Sub County Hospital	37	National HIV Reference Lab	9.8	495.0	3090	0.109	45.9	3630.9	8.6
24	22094	Kisumu Central Sub County	Maygo Dice	0	Jaramogi Oginga Odinga Teaching & Referral	2.7	2.1	210	0.983	412.7		
25	14129	Kisumu Central Sub County	Star Maternity & Nursing Home	1	Jaramogi Oginga Odinga Teaching & Referral	2.7	2.3	210	0.983	412.7	625.0	1.5
26	13534	Kisumu East Sub County	Disciples of Mercy Clinic	3	Jaramogi Oginga Odinga Teaching & Referral	2.7	9.8	210	0.983	412.7	632.5	1.5
27	13647	Kisumu East Sub County	Gita Sub County Hospital	2	Jaramogi Oginga Odinga Teaching & Referral	2.7	13.4	210	0.983	412.7	636.1	1.5
28	13591	Kisumu East Sub County	Got Nyabondo Health Centre	1	Jaramogi Oginga Odinga Teaching & Referral	2.7	9.8	210	0.983	412.7	632.5	1.5
29	13689	Kisumu East Sub County	Kibos Sugar Research Dispensary	1	Jaramogi Oginga Odinga Teaching & Referral	2.7	10.7	210	0.983	412.7	633.4	1.5
30	22354	Kisumu East Sub County	Kisumu Specialist Hospital	0	Jaramogi Oginga Odinga Teaching & Referral	2.7	11.9	210	0.983	412.7		
31	14088	Kisumu East Sub County	Simba Opepo Health Centre	1	Jaramogi Oginga Odinga Teaching & Referral	2.7	8.9	210	0.983	412.7	631.6	1.5
32	14120	Kisumu East Sub County	St Monica Hospital	11	AMPATH Care Lab, Eldoret	2.8	156.0	210	0.986	414.2	780.2	1.9
33	13890	Kisumu East Sub County	Nyalunya Health Centre	4	Jaramogi Oginga Odinga Teaching & Referral	2.7	15.0	210	0.983	412.7	637.7	1.5
34	13977	Kisumu East Sub County	Olps Clinic	6	AMPATH Care Lab, Eldoret	2.8	159.0	210	0.986	414.2	783.2	1.9
35	13524	Kisumu East Sub County	Chiga Dispensary	0	Jaramogi Oginga Odinga Teaching & Referral	2.7	15.5	210	0.983	412.7		
36	13579	Kisumu East Sub County	GK Prisons Dispensary (Kibos)	2	KEMRI CDC HIV/R Lab, Kisumu	2.7	6.6	210	0.970	407.4	624.0	1.5

Part 2: Formative Qualitative Research

Focus Group

The focus was on informing the DRT modeling inputs, outputs, and format, covering decision-making factors for POC technology placement, prioritization of POC machines. We recruited policymakers from county Ministry of Health teams, implementing partners, and laboratory leaders, and FGDs were conducted on Zoom in English by a trained facilitator. A set of a *priori* suggested model inputs informed the FGD guide, based on the co-authors' understanding of DRT systems in Kenya and engineering expertise.

Formative Input

In 2021, we conducted two virtual focus group discussions with 12 HIV treatment stakeholders, comprising representatives from county ministries of health and implementing partners. Participants had experience managing clinical teams that utilized VL and DRT results for patient management, coordinating laboratory logistics, and regulatory or budgetary decision-making. A detailed description of participant demographics is provided in Supplementary Table 3 (The table is also provided as Supplementary Table 2 in our VL modeling paper).

Overall, the processes and factors that would influence their decisions of where to place POC machines for DRT were similar to those identified for POC machines for VL testing. Generally, the decision-making process would require engagement with various stakeholders at multiple levels, from county assemblies and committees, to implementing partners, to civil society organizations. Factors that influenced participants' decisions on POC machine placement for DRT included staffing volume, facility capacity and training, geographic accessibility, disease prevalence, patient volume, and infrastructure, such as electricity and back-up power. When prioritizing the placement of POC machines, participants considered various factors such as high-volume facilities, accessibility to peripheral facilities, trained staff, and laboratory and power infrastructure. These considerations were particularly important for facilities with a high proportion of adolescents and young people who were failing to adhere to treatment.

Specifically, in reflecting on how these considerations might vary for decisions related to the placement of yet-to-be developed POC DRT machines, the emphasis on the above factors shifted slightly. When considering the placement of POC DRT machines, participants emphasized the importance of large sample volumes, accessibility to other facilities and central labs, a consistent supply of reagents, and a high-level multidisciplinary team that can run and interpret drug resistance test results.

Part 3: Mathematical Formulation for Queueing and Optimization Models

Notations

$I = 146$: the number of facilities collecting samples
$J = 5$: the total number of all 4 selected hubs and 1 national laboratory
d_i: the demand at i-th facility per working day (7 hours/day)
λ_j: mean arrival rate for service (testing) site j
μ_j: mean service rate for service (testing) site j
s_j: number of servers for service (testing) site j
$\rho_j = \lambda_j/(s_j\mu_j)$: utilization ratio for service (testing) site j ($\rho_j < 1$).
B_j: the batching delay time for service (testing) site j
T_{ij}: the transportation time from facility i to service (testing) site j
W_j: the expected time in service site j

Expected waiting time in Queueing Theory

M/M/s is one of the most widely studied queueing models, indicating that both the interarrival time distribution and service time distribution are Markovian (i.e., exponentially distributed). Here we used a M/M/s queue to model the arrival and processing of DR testing samples at selected hubs and national laboratory. An M/M/s queueing model has the following analytical solution for the expected time spent in the system. The mathematical formula of the expected waiting time is shown below. The mean arrival rate in service site j is $\lambda_j = \sum_{i=1}^{I} d_i x_{ij}$. The idle probability in service site j can be calculated as P_{0j}, where

$$P_{0j} = \frac{1}{\sum_{n=0}^{s_j-1} \frac{(\lambda_j/\mu_j)^n}{n!} + \frac{(\lambda_j/\mu_j)^{s_j}}{s_j!}\left(\frac{1}{1-\rho_j}\right)}$$

Then, in conclusion, the expected waiting time for service site (hubs or central labs) j, i.e., W_j is:

$$W_j = \frac{P_{0j}{\lambda_j}^{s_j}}{(s_j-1)!\,{\mu_j}^{s_j-1}(s_j\mu_j-\lambda_j)^2} + \frac{1}{\mu_j}$$

Optimization Formulation

For modeling and optimizing the referral network, we let $I = 146$ be the number of facilities collecting samples, and $J = 5$ be the total number of selected hubs and national laboratory. To optimize the transportation cost and batching cost through re-arranging the referral network, we formulate the following optimization problem. The mathematical formula of the optimization model is shown below. Since we want to optimize the referral network and select additional hubs, the decision variables are x_{ij}.

$$x_{ij} = \begin{cases} 1, \text{if } i^{th} \text{ facility sends samples to } j^{th} \text{ testing site} \\ 0, \text{otherwise} \end{cases}$$

The objective function is to minimize the total turnaround time of the system, including the total transportation time, total batching time, and total waiting time. Notice from the following objective, the total transportation time and total batching time are linear functions of the decision variables, while the waiting time is a non-linear function of the decision variables. The objective is shown by the formula below:

$$\min_{x_{ij}} \sum_{i=1}^{I}\sum_{j=1}^{J} x_{ij}T_{ij} + \sum_{i=1}^{I}\sum_{j=1}^{J} x_{ij}B_j + \sum_{i=1}^{I}\sum_{j=1}^{J} x_{ij}W_j$$

In the Excel tool, we only optimized the linear part of the objective due to computational complexities. This allows us to optimize the objective using 'Opensolver', an open-source Excel VBA add-in. Of note, in our Excel tool, we also set the maximum utilization for national laboratory as 0.9 and selected hubs as 0.7 to avoid overcrowding, which may incur extremely long wait time. In addition, we also have two constraints for the solutions. First, each

facility only sends samples to one service site. Second, the total number of accepted samples in each selected site should not exceed its capacity. Mathematically, those constraints can be expressed as the following forms.

$$\sum_{j=1}^{J} x_{ij} = 1 \quad \text{for } i = 1, \dots, I$$

$$\sum_{j=1}^{J} x_{ij} d_i \leq s_j \mu_j \quad \text{for } j = 1, \dots, J$$

Part 4: Excel Decision Support Tool

To provide a user-friendly interface for policymakers on mainstream computer systems, we organized the model in Excel and relied on the Opensolver add-in to solve the optimization part. According to the description on the Opensolver website (https://opensolver.org/), our Excel tool should be available for most Windows and Mac OS computers. Our Excel tool has eight different tabs, and to explore the full function of the tool, users may use 4 steps outlined here. To maximize user-friendliness focused on simplicity, clarity, and minimal opportunity to make an irrecoverable error, we created a "locked" version of the model in which users cannot manipulate any data on the second through fifth categories of tabs. The "unlocked" version is also available if users need to update user inputs.

Step 1: Parameters Input
Go to the "Basic Inputs & Model Outputs" and "Advanced Inputs Changes" tabs to change the basic and advanced parameters settings. We differentiated the two tabs of Inputs to improve the usability of the tool. Frequently changed parameters settings are incorporated into the basic tab. In addition, the main results, including expected waiting time at selected hubs and national laboratory. (Supplementary Figure 2, Panel A).

Step 2: Predetermined Parameters (Most users can skip this step)
In the "distance_matrix" and 'transportation_time_matrix' tabs, we provide the transportation data collected from Google Map, including the distance between each facility to selected labs and the national laboratory and the estimated time for transportation. In "M|M|s" tab, we show the parameters for different queues; advanced users could change the service rate according to their local knowledge. In "M|M|s calculation" tab, the users could see the detailed calculation and main output of each queueing system.

Step 3: Solving the Model
Go to the "Programming" tab, the users could see the way we lay out the optimization model and could also rerun the model using the 'OpenSolver' package. Since only 5 referral labs are incorporated in the DR testing system, users can achieve the optimized results in seconds.

Step 4: Check results
In the "Referral Network" tab, users could find detailed information for all 146 facilities, including their names, demand data, referral testing labs to send their samples under the optimized model, the simulated expected waiting time, transportation time and total turnaround time. (Supplementary Figure 2, Panel B).

Reference:
[1] Introduction to Operations Research, by Frederick Hillier, 10th edition, 2014.

Revised Standards for Quality Improvement Reporting Excellence (SQUIRE 2.0)
September 15, 2015

Text Section and Item Name	Section or Item Description
Notes to authors	• The SQUIRE guidelines provide a framework for reporting new knowledge about how to improve healthcare • The SQUIRE guidelines are intended for reports that describe system level work to improve the quality, safety, and value of healthcare, and used methods to establish that observed outcomes were due to the intervention(s). • A range of approaches exists for improving healthcare. SQUIRE may be adapted for reporting any of these. • Authors should consider every SQUIRE item, but it may be inappropriate or unnecessary to include every SQUIRE element in a particular manuscript. • The SQUIRE Glossary contains definitions of many of the key words in SQUIRE. • The Explanation and Elaboration document provides specific examples of well-written SQUIRE items, and an in-depth explanation of each item. • Please cite SQUIRE when it is used to write a manuscript.
Title and Abstract	
1. Title	Indicate that the manuscript concerns an initiative to improve healthcare (broadly defined to include the quality, safety, effectiveness, patient-centeredness, timeliness, cost, efficiency, and equity of healthcare)
2. Abstract	a. Provide adequate information to aid in searching and indexing b. Summarize all key information from various sections of the text using the abstract format of the intended publication or a structured summary such as: background, local problem, methods, interventions, results, conclusions
Introduction	*Why did you start?*
3. Problem Description	Nature and significance of the local problem
4. Available knowledge	Summary of what is currently known about the problem, including relevant previous studies

5. Rationale	Informal or formal frameworks, models, concepts, and/or theories used to explain the problem, any reasons or assumptions that were used to develop the intervention(s), and reasons why the intervention(s) was expected to work
6. Specific aims	Purpose of the project and of this report
Methods	*What did you do?*
7. Context	Contextual elements considered important at the outset of introducing the intervention(s)
8. Intervention(s)	a. Description of the intervention(s) in sufficient detail that others could reproduce it b. Specifics of the team involved in the work
9. Study of the Intervention(s)	a. Approach chosen for assessing the impact of the intervention(s) b. Approach used to establish whether the observed outcomes were due to the intervention(s)
10. Measures	a. Measures chosen for studying processes and outcomes of the intervention(s), including rationale for choosing them, their operational definitions, and their validity and reliability b. Description of the approach to the ongoing assessment of contextual elements that contributed to the success, failure, efficiency, and cost c. Methods employed for assessing completeness and accuracy of data
11. Analysis	a. Qualitative and quantitative methods used to draw inferences from the data b. Methods for understanding variation within the data, including the effects of time as a variable
12. Ethical Considerations	Ethical aspects of implementing and studying the intervention(s) and how they were addressed, including, but not limited to, formal ethics review and potential conflict(s) of interest
Results	*What did you find?*
13. Results	a. Initial steps of the intervention(s) and their evolution over time (*e.g.*, time-line diagram, flow chart, or table), including modifications made to the intervention during the project b. Details of the process measures and outcome c. Contextual elements that interacted with the intervention(s) d. Observed associations between outcomes, interventions, and relevant contextual elements e. Unintended consequences such as unexpected benefits, problems, failures, or costs associated with the intervention(s). f. Details about missing data
Discussion	*What does it mean?*
14. Summary	a. Key findings, including relevance to the rationale and specific aims b. Particular strengths of the project

15. Interpretation	a. Nature of the association between the intervention(s) and the outcomes b. Comparison of results with findings from other publications c. Impact of the project on people and systems d. Reasons for any differences between observed and anticipated outcomes, including the influence of context e. Costs and strategic trade-offs, including opportunity costs
16. Limitations	a. Limits to the generalizability of the work b. Factors that might have limited internal validity such as confounding, bias, or imprecision in the design, methods, measurement, or analysis c. Efforts made to minimize and adjust for limitations
17. Conclusions	a. Usefulness of the work b. Sustainability c. Potential for spread to other contexts d. Implications for practice and for further study in the field e. Suggested next steps
Other information	
18. Funding	Sources of funding that supported this work. Role, if any, of the funding organization in the design, implementation, interpretation, and reporting

Table 2. Glossary of key terms used in SQUIRE 2.0. This Glossary provides the intended meaning of selected words and phrases as they are used in the SQUIRE 2.0 Guidelines. They may, and often do, have different meanings in other disciplines, situations, and settings.

Assumptions
Reasons for choosing the activities and tools used to bring about changes in healthcare services at the system level.

Context
Physical and sociocultural makeup of the local environment (for example, external environmental factors, organizational dynamics, collaboration, resources, leadership, and the like), and the interpretation of these factors ("sense-making") by the healthcare delivery professionals, patients, and caregivers that can affect the effectiveness and generalizability of intervention(s).

Ethical aspects
The value of system-level initiatives relative to their potential for harm, burden, and cost to the stakeholders. Potential harms particularly associated with efforts to improve the quality, safety, and value of healthcare services include opportunity costs, invasion of privacy, and staff distress resulting from disclosure of poor performance.

Generalizability
The likelihood that the intervention(s) in a particular report would produce similar results in other settings, situations, or environments (also referred to as external validity).

Healthcare improvement
Any systematic effort intended to raise the quality, safety, and value of healthcare services, usually done at the system level. We encourage the use of this phrase rather than "qua
which often refers to more narrowly defined approaches.

Inferences
The meaning of findings or data, as interpreted by the stakeholders in healthcare services – improvers, healthcare delivery professionals, and/or patients and families

Initiative
A broad term that can refer to organization-wide programs, narrowly focused projects, or the details of specific interventions (for example, planning, execution, and assessment)

Internal validity
Demonstrable, credible evidence for efficacy (meaningful impact or change) resulting from introduction of a specific intervention into a particular healthcare system.

Intervention(s)
The specific activities and tools introduced into a healthcare system with the aim of changing its performance for the better. Complete description of an intervention includes its inputs, internal activities, and outputs (in the form of a logic model, for example), and the mechanism(s) by which these components are expected to produce changes in a system's performance.

Opportunity costs

Loss of the ability to perform other tasks or meet other responsibilities resulting from the diversion of resources needed to introduce, test, or sustain a particular improvement initiative

Problem
Meaningful disruption, failure, inadequacy, distress, confusion or other dysfunction in a healthcare service delivery system that adversely affects patients, staff, or the system as a whole, or that prevents care from reaching its full potential

Process
The routines and other activities through which healthcare services are delivered

Rationale
Explanation of why particular intervention(s) were chosen and why it was expected to work, be sustainable, and be replicable elsewhere.

Systems
The interrelated structures, people, processes, and activities that together create healthcare services for and with individual patients and populations. For example, systems exist from the personal self-care system of a patient, to the individual provider-patient dyad system, to the microsystem, to the macrosystem, and all the way to the market/social/insurance system. These levels are nested within each other.

Theory or theories
Any "-rgeiavsionrg" account that asserts causal rela
that makes sense of an otherwise obscure process or situation (explanatory theory). Theories come in many forms, and serve different purposes in the phases of improvement work. It is important to be explicit and well-founded about any informal and formal theory (or theories) that are used.

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Optimizing HIV Drug Resistance Testing Laboratory Networks in Kenya: Insights from Systems Engineering Modeling

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Title: Optimizing HIV Drug Resistance Testing Laboratory Networks in Kenya: Insights from Systems Engineering Modeling

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ABSTRACT

Background: HIV drug resistance (DR) is a growing threat to the durability of current and future HIV treatment success. DR testing (DRT) technologies are very expensive and specialized, relying on centralized laboratories in most low- and middle-income countries (LMIC). Modelling for laboratory network with point-of-care (POC) DRT assays to minimize turnaround time (TAT), is urgently needed to meet the growing demand.

Methods: We developed a model with user-friendly interface using integer programming and queueing theory to improve the DRT system in Kisumu County, Kenya. We estimated DRT demand based on both current and idealized scenarios and evaluated a centralized-laboratory-only network and an optimized POC DRT network. A one-way sensitivity analysis of key user inputs was conducted.

Results: In a centralized-laboratory-only network, the mean TAT ranged from 8.52 to 8.55 working days, and the system could not handle a demand proportion exceeding 1.6%. In contrast, the mean TAT for POC DRT network ranged from 1.13 to 2.11 working days, with demand proportion up to 4.8%. Sensitivity analyses showed that expanding DRT hubs reduces mean TAT substantially while increasing the processing rate at national labs had minimal effect. For instance, doubling the current service rate at national labs reduced the mean TAT by only 0.0% to 1.9% in various tested scenarios, whereas doubling the current service rate at DRT hubs reduced the mean TAT by 37.5% to 49.8%. In addition, faster batching modes and transportation were important factors influencing the mean TAT.

Conclusions: Our model offers decision-makers an informed framework for improving the DRT system using POC in Kenya. POC DRT networks substantially reduce mean TAT and can handle a higher demand proportion than a centralized laboratory-only network, especially for the children and pregnant women living with HIV, where there is an immediate push to use DRT results for patient case management.

Strengths and limitations of this study:

Strengths:

- The study utilizes a novel combination of integer programming and queueing theory to develop a user-friendly model that is specifically designed for optimizing the HIV drug resistance (DR) testing laboratory network in Kisumu County, Kenya, making it a pioneering approach in the field of HIV DR management.

- It offers a comprehensive analysis by comparing a centralized-laboratory-only network with an optimized point-of-care (POC) DR testing network, thereby providing evidence-based insights into how POC DRT can enhance system performance, particularly in terms of reducing turnaround time.

Limitations:

- While the study conducts a one-way sensitivity analysis of key parameters, it may not fully capture the complex interdependencies or the impact of multiple variables changing simultaneously, which could affect the generalizability and robustness of the model under different scenarios. It also does not include costs or budget parameters.

- The study focuses on Kisumu County, Kenya, and the findings might not be directly applicable to other regions or countries with different healthcare infrastructures, HIV prevalence rates, DRT guidelines or laboratory capabilities.

1.0 INTRODUCTION

HIV drug resistance (DR) is a growing threat to the durability of current and future HIV treatment success. The World Health Organization's (WHO) most recent HIV DR report in 2021 notes high concern regarding increasing pre-treatment and acquired DR, especially among children and adolescents living with HIV. Three countries, Lesotho, Uganda, and Zambia, who conducted systematic HIV DR surveillance among children and adolescents living with HIV with viral failure demonstrated high rates of nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) (50-80%) and non-NRTI (84-97%) DR. Additionally, accumulation of new DR with continued viral failure has been documented in both adults and children, further limiting usable antiretroviral options.(1–4)

However, DR testing (DRT) technologies are very expensive and specialized, which render them a limited resource.(5,6) Most low- and middle-income countries (LMIC) rely on centralized, highly specialized laboratories and specimen transport networks to conduct DRT for a limited number of patients meeting certain criteria; current low access and high turnaround times, on the order of months, limit even further use of existing DRT options.(7) However, WHO endorses the need for expanded availability of DRT, including point-of-care (POC) options, and acknowledges that use of new HIV treatment options will only expand this need.(8) For instance, while there is marked enthusiasm for dolutegravir-containing treatment options globally,(2,9,10) resistance to dolutegravir is already emerging, stressing the need to monitor dolutegravir DR urgently in LMIC.(11–13) Novel POC, or even near POC, assays are on the horizon to help create greater accessibility to DRT and minimize the return of results challenges often resulting from a centralized testing system.(14) Our group has been involved in the field validation of one such technology called oligonucleotide ligation assay (OLA)-Simple.(15–17) Unpublished Kenya HIV program data suggest better HIV viral load (VL) results utilization at POC sites than sites supported by centralized laboratory testing systems, which might have implications for POC DRT use as well.

HIV treatment programs in LMIC are expanding VL testing for all people living with HIV, therefore, creating more opportunities to detect viral failure.(18) It is critical to determine how to create decentralized laboratory networks for DRT, possibly including POC DRT assays, to meet the anticipated increase in DRT demand. Different types of decentralized laboratory network models exist in LMIC, including for HIV VL monitoring. Example networks utilize hub-and-spoke or platform sharing.(19–21) Given the even more technical training and expertise needed to conduct HIV DRT compared to HIV VL testing alone, platform sharing is not a likely viable option for DRT shortly.

Given the urgent need to meet DRT demand and the specialized training required for staff, it would be beneficial to model a network optimization for DRT using a hub-and-spoke framework, coupled with the application of queueing theory to analyze service times. The use of optimization and queuing theory in healthcare is well-documented in high-resource settings for hospital and emergency department logistics(22–28). However, their application in resource-limited contexts, particularly for HIV care, is emerging.(29). Studies in sub-Saharan Africa highlight the prevalence of queuing issues, yet the systematic application of these models for clinical improvements is still novel(30). Additionally, the deployment of POC devices for HIV testing and treatment in such settings is gaining attention(31–33).

Thus, we aimed to develop a laboratory network optimization model based on queueing theory.First, we estimated the DRT demand for two scenarios: the current scenario of repeated VL testing with adherence counseling that leads to DRT and a more idealized scenario where DRT would be implemented under more liberal guidelines. Second, we created a model for two networks: the model of utilizing one centralized laboratory at the national level for all DRT testing for Kisumu County and an optimized network that utilized not only the national DRT laboratory but also introduced additional POC DRT hubs. We hypothesized that the second scenario with POC DRT hubs would reduce turn-around time compared to the centralized laboratory model.

2.0 METHODS

2.1 Formative Data Collection

To gather insights into Kenyan policymakers' preferences for model function and decision-making, we conducted formative qualitative research using focus group discussions (FGDs). Demographics pf FGDs participants are in Supplementary Table 1. Details and results can be found in Part 2 of Supplementary materials. We obtained ethical approval from African Medical and Research Foundation (AMREF) and Jaramogi Oginga Odinga

Teaching and Referral Hospital (JOOTRH) Institutional Review Boards (IRBs) in Kenya, as well as the University of Washington and the University of Colorado Denver IRBs in the United States, and all study procedures were in line with the Declaration of Helsinki. We identify the research topic as of importance to patients and service users. The policymakers we interviewed help us better understand their needs.

2.2 Patient and Public Involvement Statement

Our research incorporated Kenyan policymakers at the formative stage through FGDs, which informed the model's development and decision-making criteria directly relevant to patient care. These discussions were pivotal in shaping the research questions and ensuring the outcome measures reflected patient priorities and experiences.

2.3 Current DRT process and selection of POC DRT hubs

In Kisumu County's healthcare system, there are a total of 146 healthcare facilities that collect both HIV VL and DRT samples.(34) After collecting samples from patients, each facility currently sends their samples to one of three central labs (KEMRI CDC HIV/R Laboratory, AMPATH Care Laboratory, and KEMRI/Walter Reed CRC Lab) for HIV VL testing. Once results are returned, patients deemed to not reach viral suppression (defined as VL<200 copies/ml per 2022 Kenya Ministry of Health (MoH) HIV treatment guidelines) undergo discussion with a multidisciplinary team at the facilities,(35) enhanced adherence counseling, including at times directly observed therapy, assessment of and addressing any other causes of viremia, and then repeat VL testing performed three months after the initial viremic episode detection and assurance of enhance adherence efforts.(15) If the patient still has viral non-suppression at repeat VL testing, then providers consult a national-level technical working group to seek advice on DRT. Once that working group reviews the case and approves DRT, the patient is called back to the facility to have another blood sample taken for DRT. This sample is currently sent to one facility, the National Public Health Laboratory (NPHL), to conduct DRT, which it conducts for the entire country for the public sector. While private sector DRT may occur in other facilities, it likely only represents a minority of the DRT occurring in the country. For DRT, the national level laboratory NPHL utilizes Sanger 3730xl for consensus sequencing of samples, which can theoretically process up to 200 samples/day with a more realistic throughput of 100 samples/day based on the available human resource and instrumentation available.

Currently, no POC DRT options are available commercially in Kenya. Our research team has been involved with a field validation of a novel, POC DRT option called OLA-Simple.(15–17,36) From March to June 2021, we piloted this technology at two of the facilities mentioned above, KEMRI CDC HIV/R Laboratory and NPHL. Based on the technical lessons learned from that field validation, we have deemed that the current iteration of the POC DRT platform of OLA Simple still requires a high level of technical expertise and, therefore, can only be implemented at a limited number of sites, unlike many of the POC VL testing platforms. Thus, we have purposefully selected existing highly specialized laboratories for HIV that have pre- and post-PCR rooms, i.e., NPHL, the three existing HIV VL testing labs, and a fourth referral hospital laboratory to the list of potential POC DRT labs, as these facilities can maintain the technical expertise needed to run this assay. Thus, five total DRT laboratories were used to model turnaround time; from here on, we refer to the NPHL as the national laboratory and the other four as POC DRT hubs. We were also restricted to just one POC DRT machine prototype for this modeling exercise.

We provide a flowchart of the POC DRT system as Supplementary Figure 1.

2.4 DRT Rate Estimation

Estimating the demand data for DRT has proven challenging due to the structure of publicly accessible routine data and the difficulties associated with using individual-level data, including issues with patient identity tracking. In addition, missing data and inconsistencies were observed to varying degrees depending on the characteristic.(37) As a result, there are no established standards in the literature for such estimations at the country level or within smaller geographic areas.(38) It is necessary to use estimated proportion of receiving DRT among people living with HIV to approximate the DRT demand.

To incorporate a range of possibilities for the demand of DRT, we considered the following two scenarios based on the overall Kenya MoH HIV treatment guidelines (Figure 1).(35) For Scenario 1, we model the current DRT demand based on existing data on high VLs from the available data for Kisumu County from the Kenya MoH HIV VL dashboard.(39) We propose a range of demand values that includes an upper estimate based on the assumption of perfect adherence to the 2022 Kenyan guidelines. This approach is motivated by the observation that the current demand for DRT may underestimate the true need for the service. In the figure, the blocks colored blue represent the chain leading to DRT, with the green blocks showing variable rates. We computed the DRT proportion with combinations of the two varying parameters of (1) percentage of the second VL being conducted (range 25-100%) and (2) the 2nd VL being ≥1000 copies/ml (range 25-75%). The estimated proportion of receiving DRT under Scenario 1 ranges from 0.40% to 4.80%. Details of the calculation process can be found in Supplementary Table 2. For Scenario 2, we consider a more idealized case scenario where DRT is recommended earlier in algorithm management, and therefore, chose a lower VL level and earlier step in VL monitoring to conduct DRT, akin to high-income country settings, where DRT is done at first detection of viremia (e.g., DRT requested at 1st VL ≥200 copies/ml). This scenario has no variable rates. Of note, while the most recent Kenya MoH HIV treatment guidelines generally recommend using a VL cutoff threshold of ≥200 copies/ml as non-suppression, unfortunately, estimates of DRT demand are only available for VL as low as 400 copies/ml. The estimated proportion of receiving DRT under Scenario 2 is 14.62%.

2.5 Data Acquisition

Our team collected model parameter information through collaboration with Kenyan policymakers and laboratory specialists. **Table 1** lists all model parameters we used in the model, base case values, and their data sources. Note that in the table, we considered two scenarios of DRT rate. The operational parameters that can be varied for sensitivity analysis include transportation and batching parameters, queueing parameters in national laboratory and POC DRT hubs. As a base case, we assumed that samples are sent once a week to the national laboratory and daily to other POC DRT hubs by each facility, using motorbikes as the transportation mode, under average road and weather conditions.

2.6 Model: Optimization and Queueing Model

This section outlines the formulation of our optimization model, including decision variables, constraints, and objectives. The primary goal of the model is to improve the total turnaround time of the whole testing system by reorganizing the referral network. Further information about the mathematical expressions used in the model can be found in the Part 3 of Supplementary materials.

The decision variable is a binary referral indicator (i.e., 0 or 1) which connects each facility with testing demand and a potential service site. If their referral indicator is equal to 1, it means the corresponding facility sends their testing samples to that service site. Two constraints are considered for both demand and supply sides. For the demand side, there is one constraint ensuring that each testing demand is met, and the samples are assigned to only one testing facility. For the supply side, the total number of accepted samples for the national laboratory and POC DRT hubs should not exceed its capacity.

The objective of the model is to minimize the overall time it takes to process the DR testing samples across all 146 facilities. This time is made up of three parts: the time it takes for a facility to prepare and send the samples (batching delay), the time it takes for the samples to be transported to the testing site (transportation time), and the time it takes for the samples to be processed at the testing site (processing time).

The processing time in the DRT laboratories was analyzed using queueing models, which are used to represent systems that involve waiting lines. The M/M/s queueing model, one of the most widely studied models, was used to model the arrival and processing of DRT samples at each selected laboratory.(40) Two separate queues were built to reflect the processes: entering samples into the computer system and sample preparation and testing process. The processing time in the system is the sum of these two queueing times.

For practical use, we focused on optimizing two factors - batching delay time and transportation time - in the objective function. Since we do not optimize over processing time, we have introduced a pre-determined and

adjustable maximum utilization rate to avoid excessively large service times. Layout of Excel Decision Support Tool can be found in Supplementary Figure 2 and details can be found in Part 4 of Supplementary materials.

3.0 RESULTS

In the results section, we compare two networks: the first solely comprises the national laboratory, and the second incorporates four POC DRT hubs alongside the national laboratory. Both networks were evaluated against two DRT rate scenarios—scenario 1 with rates ranging from 0.4% to 4.8%, and scenario 2 with a fixed rate of 14.62%. We report the mean turnaround time for each scenario under optimized network conditions. The maximum utilization rate is heuristically set at 0.9 for the national laboratory and 0.7 for the hub.

The section is further organized as follows: Section 3.1 provides a statistical summary of the performance of the system in turnaround time under varying DRT rates (scenario parameter); in section 3.2, we visualize the facilities and referral networks on a map; and section 3.3 focuses on the sensitivity analyses for several key operational parameters.

3.1 Turnaround Time

Under the national-laboratory-only network, when DRT rate ranges from 0.4% to 1.2%, the mean turnaround time across all 146 facilities is about 9 working days, which is consistent with the current observed turnaround time (per unpublished, internal data from NPHL). However, as the DRT rate increases and reaches 1.6%, demand exceeds capacity and waiting times become excessively long, rendering the model infeasible. By contrast, when the 4 POC DRT hubs are added to the network, the mean turnaround time reduces to between 1.13 and 2.11 working days, substantially improving system efficiency. The POC DRT hubs network remains feasible until the DRT rate reaches 4.8%, at which point the addition of more POC machines or improvements to the capacity of the national laboratory would be needed to meet the DRT demand. Of note, our results show that as the DRT rate increases, the mean turnaround time exhibits a monotonically increasing trend for both networks. In the POC DRT hubs model, when POC DRT hub capacity is insufficient to meet demand, samples are re-routed to national laboratory. As presented in **Table 2**, the increase in the DRT rate to 2.4% is associated with a marked surge in the standard deviation of turnaround time from 0.05 to 0.87 working days, as well as an escalation in the maximum of turnaround time from 1.71 to 8.56 working days.

3.2 Referral Network Maps

We present a visualization of the referral network, highlighting both national laboratory and POC DRT hubs in Figure 2. The visualizations are organized into different levels of DRT rate (0.4%, 1.2%, 3.6%), each with one plot displaying the complete map encompassing all facilities in Kisumu County. When DRT rate is 3.6%, we provide an additional plot zooming into facilities surrounding Kisumu city to reflect the involvement of the national lab when DRT rate grows. The figure does not contain a panel showing the national-laboratory-only network, since all samples are directed to that laboratory. Typically, facilities forward samples to the POC DRT hub closest to their location, with exceptions arising due to limited capacity at the nearest testing hub. At DRT rates of 0.4% and 1.2%, the referral network is similar, with demand for DRT largely being handled by three POC DRT hubs (KEMRI CDC HIV/R Laboratory, KEMRI/Walter Reed CRC Laboratory, and JOOTRH). At these two levels of DRT rate, the AMPATH Care Laboratory and the national laboratory do not receive any samples from Kisumu County, presumably due to high transportation times. When the DRT rate increases to 3.6%, the referral network expands to incorporate both the AMPATH Care Laboratory and the national laboratory. More specifically, when the DRT demand proportion ranges from 0.4% to 1.6%, no facilities send samples to the national lab. However, when the proportions are 2.4%, 3.2%, and 3.6%, 2, 6, and 9 facilities out of 146, respectively, send samples to the national lab. Those facilities sending their samples to NPHL face substantially longer turnaround times due to the extended transportation and batching times.

3.3 One-Way Sensitivity Analyses

Table 3 outlines the mean turnaround time of all facilities under three different settings for each parameter, as well as their percentage change compared with the base case results. We ground these changes at a DRT rate of 1.2% with the national-laboratory only model, 1.2% with adding four POC DRT hubs model, and 3.6% with the latter model. For quick visualization, a gray scale captures the magnitude of change from base case.

We further conducted one-way sensitivity analyses on key operational parameters. Our goal was to perform these analyses using both the national-laboratory-only model and the optimized model with POC hubs, selecting different DRT rates that are feasible. Batching delay mode had the most substantial impact on the mean turnaround time in the national-laboratory-only network. Specifically, when transitioning from a weekly to a twice-a-week or daily batching delay mode, the mean turnaround time decreased by 34.3% or 80.1%, respectively. In both the national laboratory and POC DRT hubs networks, we observed that adding POC DRT machines or improving the service rate also improved the system's efficiency. For example, the addition of two machines for all existing hubs led to a 40.8% reduction in turnaround time. On the other hand, increasing the operational capacity of national laboratory had a minor impact on the mean turnaround time under all settings, suggesting that expanding the capacity of the national laboratory (e.g., by adding more machines or human resources) would not substantially improve the system's efficiency. In addition, road and weather conditions had negligible effects on the mean turnaround time in all scenarios, while transportation mode had a more substantial impact on the turnaround time, particularly with walking sample delivery—an unlikely scenario—compared to a base case of motorbike transport (93.5% slower). However, car transport was not meaningfully better (only 2.7% faster) compared to motorbike transport.

4.0 DISCUSSION

Our modeling study, employing systems engineering methodologies, reveals that POC DRT is likely to be required in addition to centralized laboratory testing to realize the demand for DRT in LMICs in the upcoming years. The existing strategy, in which a solitary national laboratory is responsible for conducting DRT for the entire laboratory network, will rapidly encounter capacity limitations if the DRT demand were to merely triple from 0.4% to 1.2%. The new configuration of a POC DRT network is designed to accommodate up to a ninefold escalation in the current rate, from 0.4% to 3.6%. As noted previously, despite marked enthusiasm for dolutegravir-containing regimen use in LMICs, DR will be an enduring concern. DR to dolutegravir is already emerging,(9,41–45) and because it remains unclear what regimens should be utilized in cases of dolutegravir resistance, the use of DRT is only going to increase as surveillance for dolutegravir resistance intensifies in LMICs. Though the maximum potential DRT demand rate (14.6%) modeled in our Scenario 2 is highly improbable to occur in LMICs in the foreseeable future, there is a pressing need for a substantial increase in centralized and POC DRT capacity to cope with the likely upsurge in DRT demand. This increase in capacity will be critical to ensuring that LMICs are able to effectively manage the growing need for HIV DR test especially among the children and pregnant women living with HIV that are more sensitive to return of results.

One of the largest determinants of turnaround time was the batching delay. For instance, increasing the sample transportation frequency from a weekly to a twice-weekly basis could potentially halve the turnaround time. Furthermore, if samples were transported daily, the turnaround time could be halved once again, potentially resulting in more efficient and timely processing of samples. Of course, a trade-off between the cost and labor of frequent shipment against economies of scale of batching need to be considered when determining the batching delay for transport of samples from a spoke to a hub facility. By having closer POC DRT facilities to the spoke facilities than the national laboratory, this issue of batching delay is overcome by a network that includes POC DRT hubs. Since direct data about the impact of POC DRT testing on results utilization has not been studied, parallels with POC VL testing may be useful: although POC VL testing has not necessarily consistently improved viral suppression,(46–48,21) improved turnaround times are highly motivating for providers and patients(49) and results utilization appears to improve as well.(20,47,50)

Another important factor influencing turnaround time is the service rate or operational capacity of POC machines. This expansion of POC machines may lead to very efficient and timely delivery of test results (possibly within one day). However, our study suggests that augmenting the operational capacity of the national laboratory does not have a substantial impact on reducing the mean turnaround time for DRT. This is because facilities continue to experience substantial delays due to the long transport and batching delays involved in sending samples to the national laboratory. Furthermore, since the national laboratory has a limited capacity share reserved for Kisumu County to process samples from other parts of the country, it is fundamentally limited in improving turnaround times for the region. While we did not explicitly model the additive improvements in both increasing the operational capacity at the centralized laboratory and reducing the batching delays, were those factors more easily modifiable for a given national laboratory, it is possible that a national laboratory network could be

responsive to the increasing needs of increasing DRT demand over time. Therefore, decision-makers should consider focusing on optimizing POC machine capacity as a potentially more effective approach to improve the overall performance of the DRT network.

Given our findings, we suggest that decision makers should prioritize the introduction of POC DRT machines to meet the current and anticipated demand for DRT in Kisumu County.(51) This would effectively reduce the turnaround time and offer several programmatic advantages. POC has been shown to increase patient satisfaction and adherence,(52) reducing healthcare costs by minimizing multiple clinic visits for result inquiries(53). Implementing POC DRT hubs may address access disparities for marginalized communities facing limited investments, as we have shown with POC VL hubs[3].(31) It also ensures proper chain of custody, mitigating specimen rejection and errors in centralized referral networks.(54,55) Onsite POC testing significantly reduces the risk of poor results, enhancing clinical follow-up and confidence in laboratory systems. Additionally, it may be beneficial for decision makers to explore the possibility of improving the frequency of batching samples to the national laboratory and substantially increasing the service rate of POC machines as potential next steps to further enhance the system's paerformance.

Despite unique insights yielded by our model, there are several limitations to this work. First, one of the biggest challenges in selecting POC DRT hubs for DRT is the intrinsic laboratory capacity for that hub to handle the more technical elements related to HIV DR vs. VL testing. This immediately limits the pool of candidate hubs to a few select facilities already functioning at a relatively high laboratory capacity. Second, the model utilizes VL demand data from 2019, as more recent data may be affected by COVID-19-related VL testing reagent shortages. Third, we emphasize only time delays; however, the budget of machine installment, staff training and development programs have not been considered in this model, necessitating a further cost-effectiveness analysis. Fourth, future models could model clinical decision-making parameters, such as results utilization, to better demonstrate utility of such models.Fifth, this model is limited to the service delivery level of Kisumu County and would require expansion for it to be applicable in other counties. Finally, our formative work was limited to two focus groups with 12 total participants. On face value, this may have failed to reach thematic saturation or identify other model inputs or attributes that were desirable to decision-makers. However, the source population of individuals who make the types of resource allocation decisions targeted by this model is reasonably small. We elected to have a smaller sample size that included individuals whose scope of work is directly related to the model question.

5.0 CONCLUSIONS

In conclusion, our findings provide a valuable framework for improving the current DRT laboratory network system in Kenya, offering decision makers an opportunity to identify ways forward for DRT demand estimation, optimal referral networks and identifying key factors like transportation delays and operational capacity of POC DRT hubs. As the demand for DRT is expected to increase, we recommend the inclusion of POC DRT hubs to handle a larger volume of samples within an acceptable turnaround time.

Table 1: Model parameters, assumptions, and data sources.

Parameter	Base Case Value	Note
HIV VL test demand (per working day)		
HIV VL Testing demand in 146 facilities	Ranges from 0 to 37 (per working day) for different facilities	The quantity of VL samples from each facility is determined through the HIV client volume data from 2019 in Kisumu County's DHIS II. This was necessary because of the COVID-19 pandemic-related interruptions in 2020 and the subsequent nationwide interruptions in VL testing. Details of these estimations can be found in our related work on HIV VL testing.(31) Data Source: http://kmhfl.health.go.ke/ and https://dhis2.org/
DRT rate		
Scenario 1	0.40%~4.80%	Proportion of valid VL tests unsuppressed at VL≥1000 copies/ml threshold * Percentage completing second VL testing * Percentage of second VL≥1000 copies/ml. Calculation process with parameters combinations can be found in Supplementary Table 2 and details of the data source can be found in Supplementary Table 3. Data Source: https://viralload.nascop.org/
Scenario 2	14.62%	Proportion of valid VL tests unsuppressed at VL≥ 200 copies/ml threshold. Of note, we changed the threshold from newly recommended 200 to 400 copies/ml since the data provided does not enumerate values at the 200 copies/ml threshold.(35)
HIV DR test demand (per working day)		
HIV DRT demand in 146 facilities under Scenario 1	Minimum demand is 0; maximum demand ranges from 0 to 2	HIV VL test demand * DRT rate
HIV DRT demand in 146 facilities under Scenario 2	Ranges from 0 to 5	
Transportation		
Distance between all facilities to the national laboratory and POC DRT hubs (km)	0 to 370	We used Google Map API to collect the distance and time data given the name of facilities in Kisumu, Kenya and the locations of the national laboratory and hubs. (https://developers.google.com/maps)
Speed: (km/hour)	5 (walk), 20 (bike), 40 (motorbike), 50 (car)	To calculate the transportation time, we provided different types of transportation modes and allowed the user to decide which one to use and estimated the average speed for each transportation mode.
Road condition adjustment coefficient	0.8 (good), 1 (average), 1.2 (bad)	We considered different weather and road conditions and allowed users to change these conditions based on their needs. The weather and road conditions are 'good', 'average' or 'bad', and the time needed for transportation could be less given better weather and road conditions.
Weather condition adjustment coefficient	0.8 (good), 1 (average), 1.2 (bad)	
Batching delay (min): [frequency with which samples are transported to testing facility (hub or national laboratory)]		
Immediately	0	If the samples are sent immediately once received at the facility due to the scarcity of the demand, we would simply remove the aspect of batching. We assumed that each working day has 7 hours. If the samples are sent daily, the average delay time is half of the working day, which is 3.5 (hours), i.e., 210 minutes. If the samples are sent twice a week, the average delay is a whole day and a working day, which is 24+7 = 31 hours, i.e., 1860 minutes. If the samples are sent only once a week, the average delay is half of 4 whole days and a working day, which is (24*4+7)/2=51.5 hours, i.e., 3090 minutes. As a base case, we assume that the samples are sent daily to DRT hubs and once a week to the
Daily*	210	
Twice a week	1860	
Once a week**	3090	

		national laboratory.
National laboratory (NPHL) queueing parameters		
Entering process		
Mean service rate (test per day)	100	Mean service rate refers to the average number of DR samples received at one central laboratory given current staffing and process steps. Number of servers refers to the number of workers processing the entering of samples. We assume that there are two workers in each central laboratory working on entering the samples into the system.
Number of servers	2	
Machine process		
Mean service rate (test per day)	100	We assume each central laboratory can handle up to 500 samples per week, which in turns to be 100 samples per working day. Estimates based on personal communication with central laboratory managers. Users can adjust the service rate to account for machine downtimes due to maintenance, failure, etc.
Number of machines at each central lab	1	Estimates based on personal communication with central laboratory managers.
Percentage of capacity for DRT	100%	It is possible that a POC DRT assay could be used as a multi-disease or multi-diagnostic tool, such as those that exist for HIV VL, tuberculosis, and other infectious disease testing (e.g., GeneXpert platforms). While set at 100%, the percentage allocation of service for HIV DRT vs. another disease or diagnostic use can be modified here.
Percentage of DRT samples from Kisumu	7.9%	For 2021, 89 of 1123 DRT samples (7.925%) were from Kisumu County per personal communication with central laboratory managers.
POC DRT hub queueing parameters		
Entering process		
Mean service rate (test per day)	100	Mean service rate refers to the average number of DR samples received at DRT hubs given current staffing and process steps. We assume that there is only one worker in each hub working on entering the samples into the system.
Number of servers	1	
Machine process		
Mean service rate (tests per day)	2	Data source: personal communication with implementing partner director for HIV programs in Kisumu County. OLA DR assay can only do two samples per working day.
Number of servers		
Hub 1: KEMRI CDC	2	Number of servers refers to the number of POC DRT machines assigned for each hub.
Hub 2: AMPATH	2	
Hub 3: Walter Reed CDC	2	
Hub 4: JOORTH	2	
Percentage of samples from Kisumu		
KEMRI CDC	100%	Given that the POC DRT hubs conduct POC DRT, we assumed all samples coming to these hubs are from facilities within Kisumu County. Of note, because POC DRT will likely be based on point mutation detection, and not full genome sequencing, some of the samples with positive findings on POC DRT may need full genomic
AMPATH	100%	
Walter Reed CDC	100%	

JOOTRH	100%	sequencing via consensus sequencing at the national, central laboratory. Our DRT demand estimates, and modeling parameters do not account for these few additional DRT samples that may be needed at the national, central laboratory.

* represents base case batching delay mode of sending samples to DRT hubs
** represents base case batching delay mode of sending samples to national laboratory

Table 2: Statistics summary of mean turnaround time for two networks under various DRT demand proportion.

		National Laboratory Only		National Laboratory & POC DRT hubs	
Scenarios	**DRT Proportion**	**Turnaround time, working days Mean (SD)**	**Turnaround time, working days Min, Max**	**Turnaround time, working days Mean (SD)**	**Turnaround time, working days Min, Max**
Scenario 1	0.4%	8.52 (0.09)	8.33, 8.70	1.13 (0.07)	1.03, 1.30
	0.8%	8.53 (0.09)	8.33, 8.71	1.35 (0.2)	1.04, 1.65
	1.2%	8.55 (0.09)	8.36, 8.73	1.44 (0.15)	1.16, 1.70
	1.6%	Infeasible		1.53 (0.05)	1.46, 1.71
	2.4%	Infeasible		1.69 (0.87)	1.48, 8.56
	3.2%	Infeasible		1.90 (1.49)	1.48, 8.60
	3.6%	Infeasible		2.11 (1.81)	1.49, 8.67
	4.8%	Infeasible		Infeasible	
Scenario 2	14.62%	Infeasible		Infeasible	

Table 3: Results for one-way sensitivity analyses, with mean and standard deviation of turnaround time in working days, and the percentage change from the base case parameter.

	National-laboratory-only (DRT rate: 1.2%)	National laboratory & POC DRT hubs (DRT rate: 1.2%)	National laboratory & POC DRT hubs (DRT rate: 3.6%)
Capacity Improvement			
Improving operation capacity of the national lab			
current service rate *	8.55 (0.09)	1.44 (0.15)	2.11 (1.81)
1.5 times current service rate	8.52 (0.09), -0.4%	1.44 (0.15), 0.0%	2.07 (1.81), -1.9%
2 times current service rate	8.52 (0.09), -0.4%	1.44 (0.15), 0.0%	2.07 (1.80), -1.9%
Add POC DRT machines in hubs			
No additional machines *	**	1.44 (0.15)	2.11 (1.81)
Add 1 server for all existing hubs	**	1.23 (0.12), -14.6%	1.47 (0.90), -30.3%
Add 2 servers for all existing hubs	**	1.12 (0.07), -22.2%	1.25 (0.05), -40.8%
Improving operation capacity of hubs			
current service rate*	**	1.44 (0.15)	2.11 (1.81)
2 times current service rate	**	0.90 (0.07), -37.5%	1.06 (0.05), -49.8%
4 times current service rate	**	0.73 (0.06), -49.3%	0.79 (0.08), -62.6%
Batching delay of sending samples to the national lab			
Daily	1.70 (0.09), -80.1%	1.44 (0.15), 0.0%	1.61 (0.11), -23.7%
Twice a week	5.62 (0.09), -34.3%	1.44 (0.15), 0.0%	1.89 (1.06), -10.4%
Once a week*	8.55 (0.09)	1.44 (0.15)	2.11 (1.81)
Transportation parameters			
Road/weather condition			
Good	8.32 (0.07), -2.7%	1.43 (0.15), -0.7%	2.06 (1.76), -2.4%
Average *	8.55 (0.09)	1.44 (0.15)	2.11 (1.81)
Bad	8.78 (0.11), 2.7%	1.46 (0.15), 1.4%	2.13 (1.87), 0.9%
Transportation mode			
Walk	16.54 (0.73), 93.5%	2.04 (0.48), 41.7%	3.38 (3.73), 60.2%
Bike	9.69 (0.18), 13.3%	1.53 (0.17), 6.3%	2.29 (2.08), 8.5%
Motorbike *	8.55 (0.09)	1.44 (0.15)	2.11 (1.81)
Car	8.32 (0.07), -2.7%	1.43 (0.15), -0.7%	2.06 (1.76), -2.4%

* represents base case parameter settings

The legend of the gray scale plot:

Gray Scale	Scale (working days)
	0~2

	2~4
	4~6
	6~8
	8~10
	≥ 10

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Sex and/or Gender Data Disaggregation
We have not pursued sex and/or gender data disaggregation for the modeling work, as none of the modeling parameters are contingent on sex and/or gender.

Author Reflexivity Statement
Has the research team engaged constructively with the reflexivity statement? [Yes.]
Have the research partners co-developed the research study? [Yes.]
Does the study address priority research questions for the LMIC partner(s)? [Yes.]
Is there a LMIC partner who is the first or last author? If not, what is the explanation? [Yes.]
How have LMIC early career researchers been incorporated as authors? [Yes, one of the first co-authors is a LMIC partner, who was instrumental in conceptualization, data procurement, and decision to submit manuscript (see more below).]
How are data shared with LMIC partners to address research needs? [The data are from LMIC settings, and the model itself is shared with LMIC partners for decision-making in LMIC settings.]
Is there open access funding to improve publication dissemination? [Yes.]

Contributorship Statement
We confirm that all authors meet the ICMJE authorship criteria. Y.W. and L.K. contributed equally to this work, with R.C.P. and L.K. spearheading the conceptualization, and L.K. also managing data procurement and provision. Data procurement was supported by N.Y., S.A.H., and P.O. Funding acquisition was secured by R.C.P. and A.D.W. (MPI). Methodological framework was developed by Y.W., S.L., A.D.W., and R.C.P., with model building and software programming being the sole responsibility of Y.W. Supervision was provided by S.L. and R.C.P., while Y.W. took charge of visualization. Overall project management and regulatory compliance were supported by S.A.H., with the same on the Kenyan side managed by P.O. The original draft was written by Y.W. and R.C.P., with all coauthors contributing to the review and editing process. The decision to submit the manuscript was made by Y.W., L.K., and R.C.P., highlighting a collaborative effort across all stages of the work.

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Ethical Approval Statement: We obtained ethical approval from African Medical and Research Foundation (AMREF) (AMREF- ESRC P545/2018) and Jaramogi Oginga Odinga Teaching and Referral Hospital (JOOTRH) Institutional Review Boards (IRBs) in Kenya (IERC/JOOTRH/126/19). All study procedures were in line with the Declaration of Helsinki.

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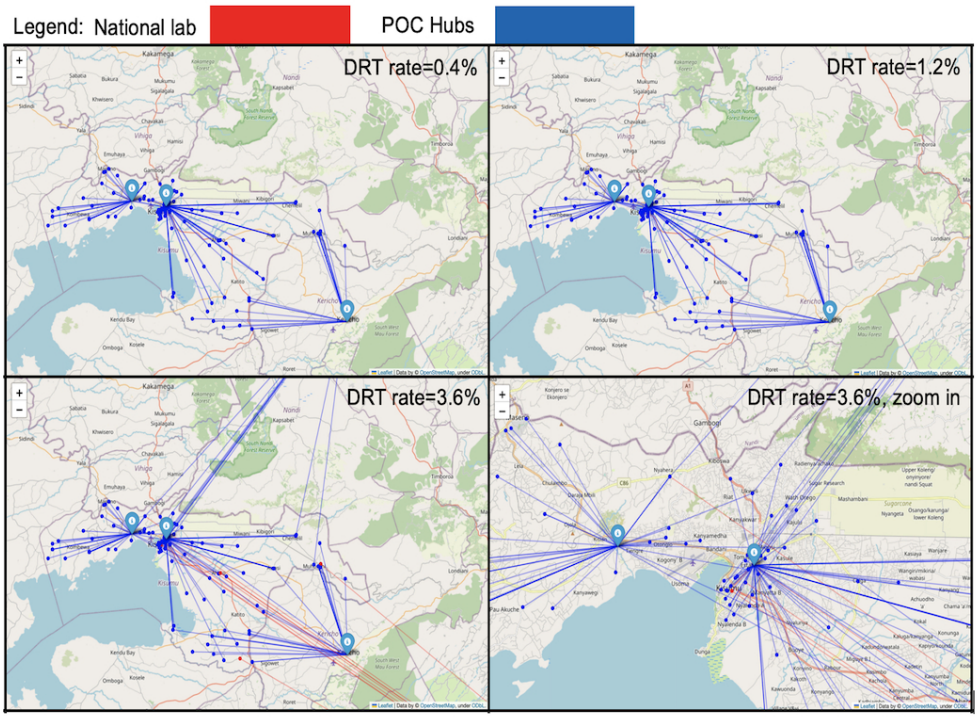
Legend of Figures

Figure 1: Scenario 1 (current DRT based on existing VL data from 2019) and 2 (more idealized DRT) flowchart for DRT demand estimation for Kisumu County, Kenya.

Note:

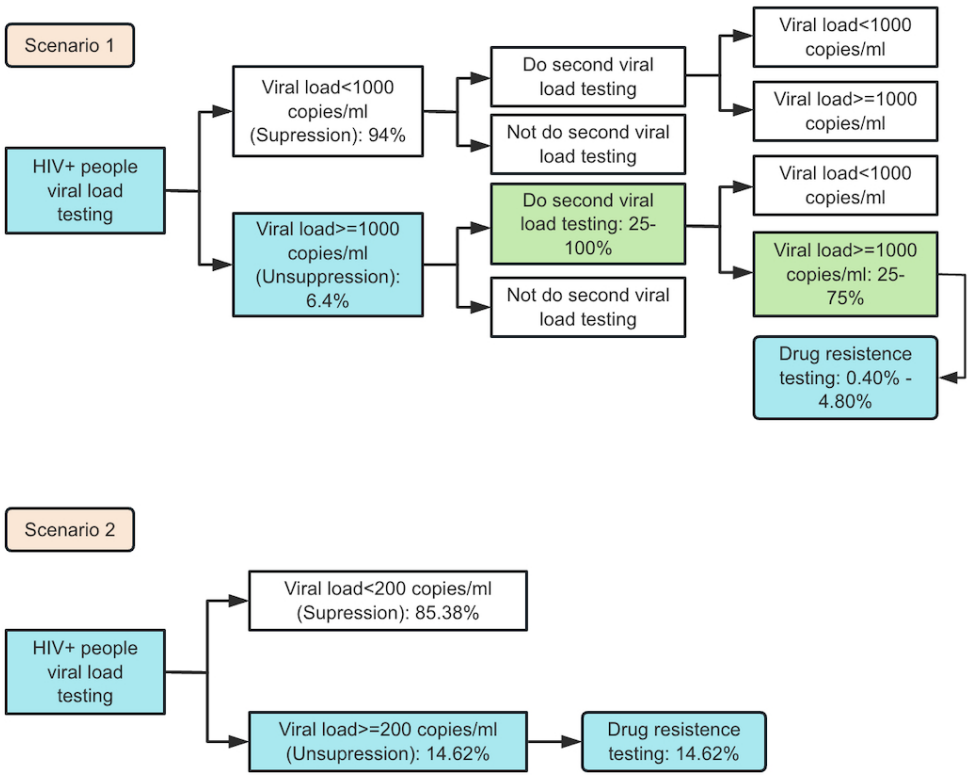
1. Color Schematic: In both Scenarios 1 and 2, blue colored blocks are utilized to illustrate the trajectory of HIV samples that lead to DRT at the final stage, in accordance with various guidelines. In Scenario 1, green colored blocks are employed to signify the consideration of various rates for conducting a second VL test and the suppressing rate for the second VL.
2. Data source: NASCOP VL database[11]. Details of data used can be found in Supplementary Table 3.

Figure 2: Referral network when POC DRT hubs are included in the testing network, with varying DRT rates and zoom levels. The markers with colors of red and blue correspond to national and four POC DRT hubs, respectively. Additionally, blue dots are used to represent 146 facilities. The network is shown through links between facilities and selected DRT laboratories.



Scenario 1 (current DRT based on existing VL data from 2019) and 2 (more idealized DRT) flowchart for DRT demand estimation for Kisumu County, Kenya.

90x90mm (300 x 300 DPI)



Referral network when POC DRT hubs are included in the testing network, with varying DRT rates and zoom levels. The markers with colors of red and blue correspond to national and four POC DRT hubs, respectively. Additionally, blue dots are used to represent 146 facilities. The network is shown through links between facilities and selected DRT laboratories.

90x90mm (300 x 300 DPI)

Supplementary Materials

Part 1: Supplementary Tables and Figures

Supplementary Table 1: Demographics of FGD participants (Number of participants: 12).

Characteristic	Median (IQR) or n (%)
Age	43 (37.5, 45)
Workstation	
County MOH	11 (92%)
Implementing partner	1 (8%)
Male	8 (67%)
Highest level of education	
Bachelor's degree	6 (50%)
Master's Degree	6 (50%)
Years of education completed	20 (19, 22)
Years working with HIV treatment monitoring	10 (9,13)
Activities related to HIV treatment monitoring currently involved in:	
Managing clinical teams that order or utilize drug resistance results for patient management	11 (92%)
Managing clinical teams that order or utilize viral load results for patient management	9 (75%)
Coordinating logistical issues for HIV laboratory tests	3 (25%)
Regulatory, validation, or verification of HIV-related machines or procedures	3 (25%)
Determining budgets	2 (17%)
Ordering and interpreting viral load for patients	1 (8%)
Ordering and interpreting drug resistance tests for patients	1 (8%)
Other coordination	1 (8%)

Note: This demographics table is also in the VL paper. (1)

Supplementary Table 2: DRT demand estimation with combinations of percentage of doing second VL testing and percentage of second VL ≥1000 copies/ml.

Proportion of patients receiving DRT	Percentage of second VL≥1000 copies/ml		
Percentage completing second VL testing	25%	50%	75%
25%	0.40%	0.80%	1.20%
50%	0.80%	1.60%	2.40%
75%	1.20%	2.40%	3.60%
100%	1.60%	3.20%	4.80%

Note: Proportion of patients receiving DRT = Proportion of valid VL tests unsuppressed at VL≥1000 copies/ml threshold * Percentage completing second VL testing * Percentage of second VL≥1000 copies/ml.

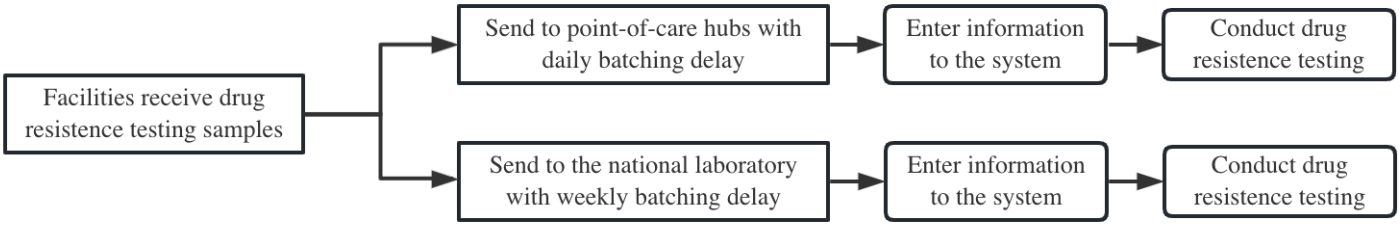
Supplementary Table 3: Parameters for estimating the DRT rate.

Total VL tests done:	**153,118**		
Routine VL Tests with Valid Outcomes:	143,323	Proportion of Routine VL Tests with Valid Outcomes:	93.60%
Viral Load ≥ 1000 copies/ml:	9,168	Proportion of Tests with Viral Load ≥ 1000 copies/ml:	6.40%
Viral Load < 1000 copies/ml:	134,155	Proportion of Tests with Viral Load < 1000 copies/ml:	93.60%
Viral Load < 400 copies/ml:	122,364	Proportion of Tests with Viral Load < 400 copies/ml:	85.38%

Viral Load 401 - 999 copies/ml:	11,791	Proportion of Tests with Viral Load 401 - 999 copies/ml:	8.23%
Confirmatory Repeat Tests:	8,042	Proportion of Confirmatory Repeat Tests:	5.25%
Viral Load ≥ 1000 copies/ml:	2,309	Proportion of Tests with Viral Load ≥ 1000 copies/ml:	28.71%
Viral Load < 1000 copies/ml:	5,733	Proportion of Tests with Viral Load < 1000 copies/ml:	71.29%
Baseline VLs:	1,753	Proportion of Baseline VLs:	1.14%
Viral Load ≥ 1000 copies/ml:	128	Proportion of Tests with Viral Load ≥ 1000 copies/ml:	7.30%
Viral Load < 1000 copies/ml:	1,625	Proportion of Tests with Viral Load < 1000 copies/ml:	92.70%

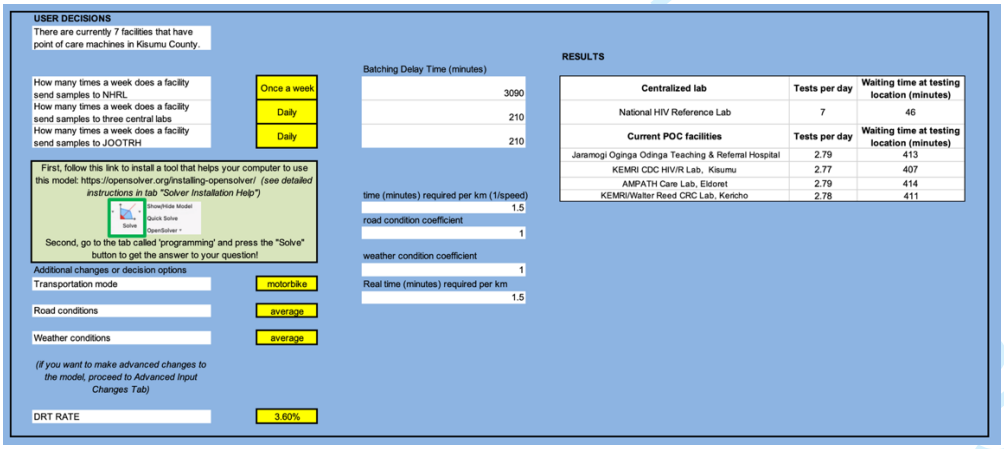
Data Source: https://viralload.nascop.org/.

Supplementary Figure 1: A flowchart for the working process of the system.



Supplementary Figure 2: Layout of Excel tool: Panel A is the tab "Basic Inputs & Model Outputs" which shows basic parameter inputs and results output, and Panel B is the tab "Referral Network" where users can find detailed information for each individual facility.

Panel A:



Panel B:

	MFL Code	Sub County	Facility Name	Total HIV test per day (7 hours)	Hub number or Central labs to go	Expected number of samples at testing location every day	Transportation Time (minutes)	Frequency at which facilities send samples for testing (daily, once a week, twice a week) (minutes)	Expected waiting time at testing location (working days)	Expected waiting time at testing location (minutes)	Total Turnaround Time (minutes)	Total turnaround time (working days)
1	13939	Kisumu Central Sub County	Jaramogi Oginga Odinga Teaching & Referral H	33	National HIV Reference Lab	9.8	496.5	3090	0.109	45.9	3632.4	8.6
2	20700	Kisumu Central Sub County	Keeping alive Society Hope	0	Jaramogi Oginga Odinga Teaching & Referral	2.7	4.7	210	0.983	412.7	627.4	1.5
3	24200	Kisumu Central Sub County	LVCT Health Manyatta Dice	0	Jaramogi Oginga Odinga Teaching & Referral	2.7	3.0	210	0.983	412.7	625.7	1.5
4	13856	Kisumu Central Sub County	Nightingale Medical Centre	2	Jaramogi Oginga Odinga Teaching & Referral	2.7	2.3	210	0.983	412.7	625.0	1.5
5	20956	Kisumu Central Sub County	AAR Health care-Kisumu	0	Jaramogi Oginga Odinga Teaching & Referral	2.7	4.5	210	0.983	412.7	627.2	1.5
6	13465	Kisumu Central Sub County	Aga Khan Hospital (Kisumu)	0	Jaramogi Oginga Odinga Teaching & Referral	2.7	3.2	210	0.983	412.7		
7	13704	Kisumu Central Sub County	Kisumu County Hospital	32	National HIV Reference Lab	9.8	495.0	3090	0.109	45.9	3630.9	8.6
8	19669	Kisumu Central Sub County	Kisumu Police Line Dispensary	0	Jaramogi Oginga Odinga Teaching & Referral	2.7	6.2	210	0.983	412.7		
9	16662	Kisumu Central Sub County	Liverpool VCT (Kisumu East)	16	National HIV Reference Lab	9.8	495.0	3090	0.109	45.9	3630.9	8.6
10	27025	Kisumu Central Sub County	Maaygo Railways	0	Jaramogi Oginga Odinga Teaching & Referral	2.7	2.1	210	0.983	412.7		
11	13808	Kisumu Central Sub County	Milimani Hospital	0	Jaramogi Oginga Odinga Teaching & Referral	2.7	5.4	210	0.983	412.7		
12	14027	Kisumu Central Sub County	Railways Dispensary (Kisumu)	7	KEMRI CDC HIV/R Lab, Kisumu	2.7	17.7	210	0.970	407.4	635.1	1.5
13	20523	Kisumu Central Sub County	Tumaini Dice Dispensary (Kisumu)	2	Jaramogi Oginga Odinga Teaching & Referral	2.7	6.2	210	0.983	412.7	628.9	1.5
14	13807	Kisumu Central Sub County	Migosi Sub County Hospital	8	AMPATH Care Lab, Eldoret	2.8	159.0	210	0.986	414.2	783.2	1.9
15	13887	Kisumu Central Sub County	Nyalenda Health Centre	2	Jaramogi Oginga Odinga Teaching & Referral	2.7	8.6	210	0.983	412.7	631.3	1.5
16	14012	Kisumu Central Sub County	Pand Pieri Community Dispensary	13	AMPATH Care Lab, Eldoret	2.8	168.0	210	0.986	414.2	792.2	1.9
17	16882	Kisumu Central Sub County	St Jones and Ring Road Health Clinic	0	Jaramogi Oginga Odinga Teaching & Referral	2.7	1.5	210	0.983	412.7		
18	13464	Kisumu Central Sub County	Administration Police Dispensary (Kisumu)	2	Jaramogi Oginga Odinga Teaching & Referral	2.7	2.9	210	0.983	412.7	625.6	1.5
19	21220	Kisumu Central Sub County	Anza Mapema Clinic	0	Jaramogi Oginga Odinga Teaching & Referral	2.7	1.7	210	0.983	412.7		
20	20123	Kisumu Central Sub County	Avenue Hospital Kisumu	0	Jaramogi Oginga Odinga Teaching & Referral	2.7	3.9	210	0.983	412.7		
21	17554	Kisumu Central Sub County	K-Met Corkran Medical Clinic	0	Jaramogi Oginga Odinga Teaching & Referral	2.7	2.4	210	0.983	412.7	625.1	1.5
22	20836	Kisumu Central Sub County	St Monica Hospital (Town Clinic)	5	KEMRI CDC HIV/R Lab, Kisumu	2.7	21.8	210	0.970	407.4	639.2	1.5
23	13738	Kisumu Central Sub County	Lumumba Sub County Hospital	37	National HIV Reference Lab	9.8	495.0	3090	0.109	45.9	3630.9	8.6
24	22094	Kisumu Central Sub County	Maaygo Dice	0	Jaramogi Oginga Odinga Teaching & Referral	2.7	2.1	210	0.983	412.7		
25	14129	Kisumu Central Sub County	Star Maternity & Nursing Home	1	Jaramogi Oginga Odinga Teaching & Referral	2.7	2.3	210	0.983	412.7	625.0	1.5
26	13534	Kisumu East Sub County	Disciples of Mercy Clinic	3	Jaramogi Oginga Odinga Teaching & Referral	2.7	9.8	210	0.983	412.7	632.5	1.5
27	13647	Kisumu East Sub County	Gita Sub County Hospital	2	Jaramogi Oginga Odinga Teaching & Referral	2.7	13.4	210	0.983	412.7	636.1	1.5
28	13591	Kisumu East Sub County	Got Nyabondo Health Centre	1	Jaramogi Oginga Odinga Teaching & Referral	2.7	9.8	210	0.983	412.7	632.5	1.5
29	13689	Kisumu East Sub County	Kibos Sugar Research Dispensary	1	Jaramogi Oginga Odinga Teaching & Referral	2.7	10.7	210	0.983	412.7	633.4	1.5
30	22354	Kisumu East Sub County	Kisumu Specialist Hospital	0	Jaramogi Oginga Odinga Teaching & Referral	2.7	11.9	210	0.983	412.7		
31	14088	Kisumu East Sub County	Simba Opepo Health Centre	1	Jaramogi Oginga Odinga Teaching & Referral	2.7	8.9	210	0.983	412.7	631.6	1.5
32	14120	Kisumu East Sub County	St Monica Hospital	11	AMPATH Care Lab, Eldoret	2.8	156.0	210	0.986	414.2	780.2	1.9
33	13890	Kisumu East Sub County	Nyalunya Health Centre	4	Jaramogi Oginga Odinga Teaching & Referral	2.7	15.0	210	0.983	412.7	637.7	1.5
34	13977	Kisumu East Sub County	Olps Clinic	6	AMPATH Care Lab, Eldoret	2.8	159.0	210	0.986	414.2	783.2	1.9
35	13524	Kisumu East Sub County	Chiga Dispensary	0	Jaramogi Oginga Odinga Teaching & Referral	2.7	15.5	210	0.983	412.7		
36	13579	Kisumu East Sub County	GK Prisons Dispensary (Kibos)	2	KEMRI CDC HIV/R Lab, Kisumu	2.7	6.6	210	0.970	407.4	624.0	1.5

Part 2: Formative Qualitative Research

Focus Group

The focus was on informing the DRT modeling inputs, outputs, and format, covering decision-making factors for POC technology placement, prioritization of POC machines. We recruited policymakers from county Ministry of Health teams, implementing partners, and laboratory leaders, and FGDs were conducted on Zoom in English by a trained facilitator. A set of a *priori* suggested model inputs informed the FGD guide, based on the co-authors' understanding of DRT systems in Kenya and engineering expertise.

Formative Input

In 2021, we conducted two virtual focus group discussions with 12 HIV treatment stakeholders, comprising representatives from county ministries of health and implementing partners. Participants had experience managing clinical teams that utilized VL and DRT results for patient management, coordinating laboratory logistics, and regulatory or budgetary decision-making. A detailed description of participant demographics is provided in Supplementary Table 3 (The table is also provided as Supplementary Table 2 in our VL modeling paper).

Overall, the processes and factors that would influence their decisions of where to place POC machines for DRT were similar to those identified for POC machines for VL testing. Generally, the decision-making process would require engagement with various stakeholders at multiple levels, from county assemblies and committees, to implementing partners, to civil society organizations. Factors that influenced participants' decisions on POC machine placement for DRT included staffing volume, facility capacity and training, geographic accessibility, disease prevalence, patient volume, and infrastructure, such as electricity and back-up power. When prioritizing the placement of POC machines, participants considered various factors such as high-volume facilities, accessibility to peripheral facilities, trained staff, and laboratory and power infrastructure. These considerations were particularly important for facilities with a high proportion of adolescents and young people who were failing to adhere to treatment.

Specifically, in reflecting on how these considerations might vary for decisions related to the placement of yet-to-be developed POC DRT machines, the emphasis on the above factors shifted slightly. When considering the placement of POC DRT machines, participants emphasized the importance of large sample volumes, accessibility to other facilities and central labs, a consistent supply of reagents, and a high-level multidisciplinary team that can run and interpret drug resistance test results.

Part 3: Mathematical Formulation for Queueing and Optimization Models

Notations

$I = 146$: the number of facilities collecting samples
$J = 5$: the total number of all 4 selected hubs and 1 national laboratory
d_i: the demand at i-th facility per working day (7 hours/day)
λ_j: mean arrival rate for service (testing) site j
μ_j: mean service rate for service (testing) site j
s_j: number of servers for service (testing) site j
$\rho_j = \lambda_j/(s_j\mu_j)$: utilization ratio for service (testing) site j ($\rho_j < 1$).
B_j: the batching delay time for service (testing) site j
T_{ij}: the transportation time from facility i to service (testing) site j
W_j: the expected time in service site j

Expected waiting time in Queueing Theory

M/M/s is one of the most widely studied queueing models, indicating that both the interarrival time distribution and service time distribution are Markovian (i.e., exponentially distributed). (2) Here we used a M/M/s queue to model the arrival and processing of DR testing samples at selected hubs and national laboratory. An M/M/s queueing model has the following analytical solution for the expected time spent in the system. The mathematical formula of the expected waiting time is shown below. The mean arrival rate in service site j is $\lambda_j = \sum_{i=1}^{I} d_i x_{ij}$. The idle probability in service site j can be calculated as P_{0j}, where

$$P_{0j} = \frac{1}{\sum_{n=0}^{s_j-1} \frac{(\lambda_j/\mu_j)^n}{n!} + \frac{(\lambda_j/\mu_j)^{s_j}}{s_j!}\left(\frac{1}{1-\rho_j}\right)}$$

Then, in conclusion, the expected waiting time for service site (hubs or central labs) j, i.e., W_j is:

$$W_j = \frac{P_{0j}{\lambda_j}^{s_j}}{(s_j-1)!\,{\mu_j}^{s_j-1}(s_j\mu_j-\lambda_j)^2} + \frac{1}{\mu_j}$$

Optimization Formulation

For modeling and optimizing the referral network, we let $I = 146$ be the number of facilities collecting samples, and $J = 5$ be the total number of selected hubs and national laboratory. To optimize the transportation cost and batching cost through re-arranging the referral network, we formulate the following optimization problem. The mathematical formula of the optimization model is shown below. Since we want to optimize the referral network and select additional hubs, the decision variables are x_{ij}.

$$x_{ij} = \begin{cases} 1, \text{if } i^{th} \text{ facility sends samples to } j^{th} \text{ testing site} \\ 0, \text{otherwise} \end{cases}$$

The objective function is to minimize the total turnaround time of the system, including the total transportation time, total batching time, and total waiting time. Notice from the following objective, the total transportation time and total batching time are linear functions of the decision variables, while the waiting time is a non-linear function of the decision variables. The objective is shown by the formula below:

$$\min_{x_{ij}} \sum_{i=1}^{I}\sum_{j=1}^{J} x_{ij}T_{ij} + \sum_{i=1}^{I}\sum_{j=1}^{J} x_{ij}B_j + \sum_{i=1}^{I}\sum_{j=1}^{J} x_{ij}W_j$$

In the Excel tool, we only optimized the linear part of the objective due to computational complexities. This allows us to optimize the objective using 'Opensolver', an open-source Excel VBA add-in. Of note, in our Excel tool, we also set the maximum utilization for national laboratory as 0.9 and selected hubs as 0.7 to avoid overcrowding, which may incur extremely long wait time. In addition, we also have two constraints for the solutions. First, each facility only sends samples to one service site. Second, the total number of accepted samples in each selected site should not exceed its capacity. Mathematically, those constraints can be expressed as the following forms.

$$\sum_{j=1}^{J} x_{ij} = 1 \quad \text{for } i = 1, \dots, I$$

$$\sum_{j=1}^{J} x_{ij} d_i \le s_j \mu_j \quad \text{for } j = 1, \dots, J$$

Part 4: Excel Decision Support Tool

To provide a user-friendly interface for policymakers on mainstream computer systems, we organized the model in Excel and relied on the Opensolver add-in to solve the optimization part. According to the description on the

Opensolver website (https://opensolver.org/), our Excel tool should be available for most Windows and Mac OS computers. Our Excel tool has eight different tabs, and to explore the full function of the tool, users may use 4 steps outlined here. To maximize user-friendliness focused on simplicity, clarity, and minimal opportunity to make an irrecoverable error, we created a "locked" version of the model in which users cannot manipulate any data on the second through fifth categories of tabs. The "unlocked" version is also available if users need to update user inputs.

Step 1: Parameters Input
Go to the "Basic Inputs & Model Outputs" and "Advanced Inputs Changes" tabs to change the basic and advanced parameters settings. We differentiated the two tabs of Inputs to improve the usability of the tool. Frequently changed parameters settings are incorporated into the basic tab. In addition, the main results, including expected waiting time at selected hubs and national laboratory. (Supplementary Figure 2, Panel A).

Step 2: Predetermined Parameters (Most users can skip this step)
In the "distance_matrix" and 'transportation_time_matrix' tabs, we provide the transportation data collected from Google Map, including the distance between each facility to selected labs and the national laboratory and the estimated time for transportation. In "M|M|s" tab, we show the parameters for different queues; advanced users could change the service rate according to their local knowledge. In "M|M|s calculation" tab, the users could see the detailed calculation and main output of each queueing system.

Step 3: Solving the Model
Go to the "Programming" tab, the users could see the way we lay out the optimization model and could also rerun the model using the 'OpenSolver' package. Since only 5 referral labs are incorporated in the DR testing system, users can achieve the optimized results in seconds.

Step 4: Check results
In the "Referral Network" tab, users could find detailed information for all 146 facilities, including their names, demand data, referral testing labs to send their samples under the optimized model, the simulated expected waiting time, transportation time and total turnaround time. (Supplementary Figure 2, Panel B).

Reference:
[1] Wang Y, Wagner AD, Liu S, et al. Using queueing models as a decision support tool in allocating point-of-care HIV viral load testing machines in Kisumu County, Kenya. Health Policy Plan. 2024;39(1):44-55. doi:10.1093/heapol/czad111

[2] Introduction to Operations Research, by Frederick Hillier, 10th edition, 2014.

Revised Standards for Quality Improvement Reporting Excellence (SQUIRE 2.0)
September 15, 2015

Text Section and Item Name	Section or Item Description
Notes to authors	• The SQUIRE guidelines provide a framework for reporting new knowledge about how to improve healthcare • The SQUIRE guidelines are intended for reports that describe system level work to improve the quality, safety, and value of healthcare, and used methods to establish that observed outcomes were due to the intervention(s). • A range of approaches exists for improving healthcare. SQUIRE may be adapted for reporting any of these. • Authors should consider every SQUIRE item, but it may be inappropriate or unnecessary to include every SQUIRE element in a particular manuscript. • The SQUIRE Glossary contains definitions of many of the key words in SQUIRE. • The Explanation and Elaboration document provides specific examples of well-written SQUIRE items, and an in-depth explanation of each item. • Please cite SQUIRE when it is used to write a manuscript.
Title and Abstract	
1. Title	Indicate that the manuscript concerns an initiative to improve healthcare (broadly defined to include the quality, safety, effectiveness, patient-centeredness, timeliness, cost, efficiency, and equity of healthcare)
2. Abstract	a. Provide adequate information to aid in searching and indexing b. Summarize all key information from various sections of the text using the abstract format of the intended publication or a structured summary such as: background, local problem, methods, interventions, results, conclusions
Introduction	*Why did you start?*
3. Problem Description	Nature and significance of the local problem
4. Available knowledge	Summary of what is currently known about the problem, including relevant previous studies

5. Rationale	Informal or formal frameworks, models, concepts, and/or theories used to explain the problem, any reasons or assumptions that were used to develop the intervention(s), and reasons why the intervention(s) was expected to work
6. Specific aims	Purpose of the project and of this report
Methods	*What did you do?*
7. Context	Contextual elements considered important at the outset of introducing the intervention(s)
8. Intervention(s)	a. Description of the intervention(s) in sufficient detail that others could reproduce it b. Specifics of the team involved in the work
9. Study of the Intervention(s)	a. Approach chosen for assessing the impact of the intervention(s) b. Approach used to establish whether the observed outcomes were due to the intervention(s)
10. Measures	a. Measures chosen for studying processes and outcomes of the intervention(s), including rationale for choosing them, their operational definitions, and their validity and reliability b. Description of the approach to the ongoing assessment of contextual elements that contributed to the success, failure, efficiency, and cost c. Methods employed for assessing completeness and accuracy of data
11. Analysis	a. Qualitative and quantitative methods used to draw inferences from the data b. Methods for understanding variation within the data, including the effects of time as a variable
12. Ethical Considerations	Ethical aspects of implementing and studying the intervention(s) and how they were addressed, including, but not limited to, formal ethics review and potential conflict(s) of interest
Results	*What did you find?*
13. Results	a. Initial steps of the intervention(s) and their evolution over time (*e.g.*, time-line diagram, flow chart, or table), including modifications made to the intervention during the project b. Details of the process measures and outcome c. Contextual elements that interacted with the intervention(s) d. Observed associations between outcomes, interventions, and relevant contextual elements e. Unintended consequences such as unexpected benefits, problems, failures, or costs associated with the intervention(s). f. Details about missing data
Discussion	*What does it mean?*
14. Summary	a. Key findings, including relevance to the rationale and specific aims b. Particular strengths of the project

15. Interpretation	a. Nature of the association between the intervention(s) and the outcomes b. Comparison of results with findings from other publications c. Impact of the project on people and systems d. Reasons for any differences between observed and anticipated outcomes, including the influence of context e. Costs and strategic trade-offs, including opportunity costs
16. Limitations	a. Limits to the generalizability of the work b. Factors that might have limited internal validity such as confounding, bias, or imprecision in the design, methods, measurement, or analysis c. Efforts made to minimize and adjust for limitations
17. Conclusions	a. Usefulness of the work b. Sustainability c. Potential for spread to other contexts d. Implications for practice and for further study in the field e. Suggested next steps
Other information	
18. Funding	Sources of funding that supported this work. Role, if any, of the funding organization in the design, implementation, interpretation, and reporting

Table 2. Glossary of key terms used in SQUIRE 2.0. This Glossary provides the intended meaning of selected words and phrases as they are used in the SQUIRE 2.0 Guidelines. They may, and often do, have different meanings in other disciplines, situations, and settings.

Assumptions
Reasons for choosing the activities and tools used to bring about changes in healthcare services at the system level.

Context
Physical and sociocultural makeup of the local environment (for example, external environmental factors, organizational dynamics, collaboration, resources, leadership, and the like), and the interpretation of these factors ("sense-making") by the healthcare delivery professionals, patients, and caregivers that can affect the effectiveness and generalizability of intervention(s).

Ethical aspects
The value of system-level initiatives relative to their potential for harm, burden, and cost to the stakeholders. Potential harms particularly associated with efforts to improve the quality, safety, and value of healthcare services include opportunity costs, invasion of privacy, and staff distress resulting from disclosure of poor performance.

Generalizability
The likelihood that the intervention(s) in a particular report would produce similar results in other settings, situations, or environments (also referred to as external validity).

Healthcare improvement
Any systematic effort intended to raise the quality, safety, and value of healthcare services, usually done at the system level. We encourage the use of this phrase rather than "quality improvement," which often refers to more narrowly defined approaches.

Inferences
The meaning of findings or data, as interpreted by the stakeholders in healthcare services – improvers, healthcare delivery professionals, and/or patients and families

Initiative
A broad term that can refer to organization-wide programs, narrowly focused projects, or the details of specific interventions (for example, planning, execution, and assessment)

Internal validity
Demonstrable, credible evidence for efficacy (meaningful impact or change) resulting from introduction of a specific intervention into a particular healthcare system.

Intervention(s)
The specific activities and tools introduced into a healthcare system with the aim of changing its performance for the better. Complete description of an intervention includes its inputs, internal activities, and outputs (in the form of a logic model, for example), and the mechanism(s) by which these components are expected to produce changes in a system's performance.

Opportunity costs

Loss of the ability to perform other tasks or meet other responsibilities resulting from the diversion of resources needed to introduce, test, or sustain a particular improvement initiative

Problem
Meaningful disruption, failure, inadequacy, distress, confusion or other dysfunction in a healthcare service delivery system that adversely affects patients, staff, or the system as a whole, or that prevents care from reaching its full potential

Process
The routines and other activities through which healthcare services are delivered

Rationale
Explanation of why particular intervention(s) were chosen and why it was expected to work, be sustainable, and be replicable elsewhere.

Systems
The interrelated structures, people, processes, and activities that together create healthcare services for and with individual patients and populations. For example, systems exist from the personal self-care system of a patient, to the individual provider-patient dyad system, to the microsystem, to the macrosystem, and all the way to the market/social/insurance system. These levels are nested within each other.

Theory or theories
Any "reason-giving" account that asserts causal relationships between variables (causal theory) or that makes sense of an otherwise obscure process or situation (explanatory theory). Theories come in many forms, and serve different purposes in the phases of improvement work. It is important to be explicit and well-founded about any informal and formal theory (or theories) that are used.