U.S. CENTERS FOR DISEASE CONTROL AND PREVENTION

20 YEARS 2002 - 2022

CELEBRATING SUSTAINABLE PARTNERSHIPS

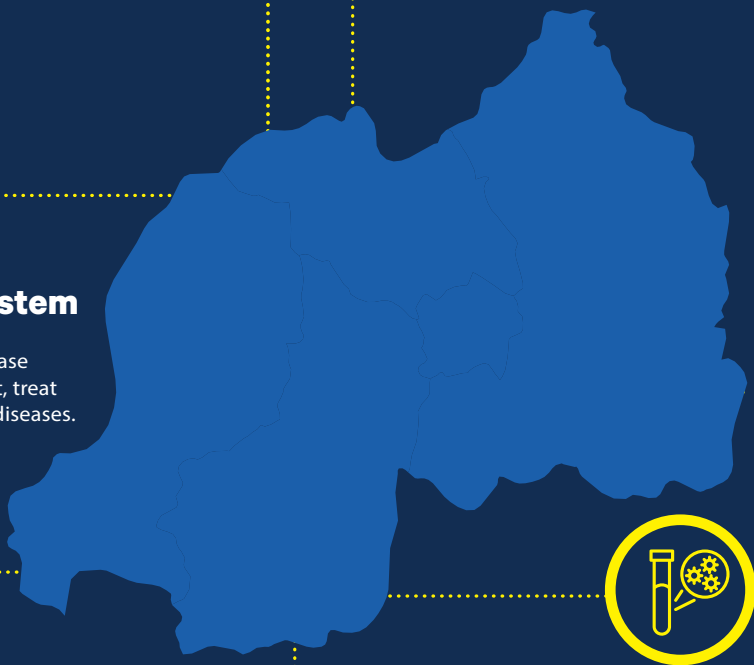
A reflection of key publications that illustrate the scientific journey of CDC's collaboration with its partners through the years.

HIV

Through PEPFAR, CDC strengthens HIV prevention, care and treatment services at government-run and faith-based health facilities to achieve and sustain HIV epidemic control.

Malaria

CDC co-implements with USAID malaria prevention and control activities through the U.S. President's Malaria Initiative (PMI) working closely with the Rwanda national malaria program.



Health Information System

CDC reinforces innovative and robust electronic health information and disease surveillance systems to prevent, detect, treat and report cases of HIV, TB, and other diseases.

Global Health Security

CDC supports the Ministry of Health with strategic planning, national outbreak preparedness, establishment of national and provincial Emergency Operations Centers and emergency management trainings for staff.

Laboratory capacity

CDC sustains enhanced laboratory Infrastructure, workforce development, and local expertise in continuous quality improvement.

FETP

With CDC support, Rwanda's Field Epidemiology Training Program (FETP) trains local epidemiologists and public health leaders to use public health surveillance data to address priority public health challenges and respond to emergencies.

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

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Partners Acknowledgement

We could not do our work without our esteemed Partners.

Foreword

The United States Centers for Disease Control and Prevention (CDC) is pleased to celebrate twenty years of collaboration between the Rwanda Ministry of Health, and several implementing partners. The collaborative work began in 2002 when CDC's Global AIDS Program established an office in Kigali to support HIV/AIDS prevention and control activities. In 2004, the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) provided significant resources allowing the office to grow in staff and expand its scope of activities. In 2007, the U.S. President's Malaria Initiative (PMI) and influenza programs were added to the portfolio. One of CDC's flagship programs, the Field Epidemiology Training Program (FETP), started in Rwanda in 2010 and with the 2018 Ebola outbreak in neighboring Democratic Republic of Congo, the office received additional support for Ebola Virus Disease preparedness activities. This global health security support continued during the recent COVID-19 pandemic to assist the Government of Rwanda (GOR) in its preparedness and response.

This report illustrates the scientific journey of the prolific collaboration between CDC and its partners while focusing on the program areas covered through the years. These scientific publications direct you to areas that have been investigated and the contributions made in understanding disease prevention, care, treatment, and the systems that were used to support these programs. It brings together studies published between 2002-2022 where CDC-Rwanda provided support through funding and/or technical assistance. The selected 12 peer-reviewed publications represent only a snapshot of 65 publications produced by this collaboration, demonstrating the achievements and advances facilitated by a successful partnership. They perfectly illustrate the variety and depth of the supported public health programs during these past 2 decades. Some of the manuscripts report on non-HIV topics such as laboratory strengthening, influenza surveillance, FETP-related lessons learned, and possible future challenges with malaria control. Most of the papers explore HIV topics, given the scope of CDC Rwanda's portfolio, such as HIV prevention, testing, care and treatment, interventions with key populations, surveillance, and tuberculosis. This compilation clearly shows that CDC Rwanda has provided valuable technical expertise in many public health areas in support of national programs.

This report is one of the key highlights to mark 20 years of CDC's work in Rwanda. Reading it will deepen one's understanding of CDC-Rwanda's contribution to generating new knowledge, improving disease programming based on the latest available science, and assisting decision makers to act on evidence-informed decisions. In essence, these manuscripts will give you an appreciation of CDC-Rwanda's contribution to the health sector in Rwanda, the region, and ultimately the entire world.

As CDC celebrates 20 years of existence in Rwanda, this presents an opportunity to reflect, evaluate and start planning on how to forge ahead. This publication is part of that moment of reflection and assessment of where we have come from, where we are, and where we are going. It shows that great progress has been made, while revealing that the final stretch demands continuous and expanded effort to cover all our program performance gaps. This will require all of us to think more strategically based on available or newly generated evidence and help direct the national program to achieve zero gaps. The strong U.S. and GOR collaboration will continue to support the ongoing journey towards ending the HIV/AIDS epidemic in this decade, while addressing other public health challenges. Global health partnerships are the cornerstone for public health responsiveness, innovation, and effectiveness. Together we have and will continue to address critical needs and build capacity for Rwanda and beyond.

Happy 20th Anniversary CDC-Rwanda

Dr. Thierry ROELS,
CDC-Rwanda Country Director

Hon. Dr. Sabin NSANZIMANA
Minister of Health, Republic of Rwanda

CDC Rwanda Timeline

2002
• Rwanda's HIV prevalence is estimated at 8%. The CDC/GAP Rwanda County Program begins working in the following strategic areas: PMTCT, Laboratory, Surveillance, M&E

2003
• CDC signs first Cooperating Agreement with MOH focused on improving HIV/AIDS service Delivery through improved HIV Surveillance, Ante-Natal Care Sentinel Surveillance and National Capacity for quality HIV care and treatment expansion.

2006
• Through PEPFAR/CDC support, the national scale-up of HIV treatment increases from about 900 PLHIV out of thousands on ART in 2002 to 32,000 in 2006.
• PEPFAR/CDC pilots the use of dried blood spot PCR tests at NRL to enable early infant diagnosis and faster response to the epidemic.

2007
• PEPFAR/CDC through ICAP improve infrastructure and equipment at all NRL/ICAP supported sites across the country.

2008
• MOH with support from CDC and in collaboration with PIH deploy the first electronic medical record system (EMR) to improve patient data management.
• Launch of FETP in Rwanda with short courses in applied epidemiology for government employees.

2010
• CDC/WHO-AFRO establish an accreditation process to build African Laboratory capacity.
• First cohort of 15 FELTP residents are enrolled in the program.
• CDC supports RBC/MOH to conduct Rwanda's 2010 national HIV/Syphilis survey among pregnant women.

2011
• Electronic Disease Surveillance and Response System launched under TRACnet II & used to monitor 23 diseases under surveillance in Rwanda.
• Cases of malaria drop from 8% in 2010 to 3% in 2011.

2015
• Rwanda's National Reference Laboratories establishes 6 additional laboratories through training and mentorship to support scale up of Viral Load testing.

• Rwanda among first countries to bring its PMTCT rates below 2% per annum, showing that it is possible to eliminate Mother to Child Transmission of HIV in Rwanda.

2016
• Incidence of TB among PLHIV dropped to 25% from 48% in 2005.

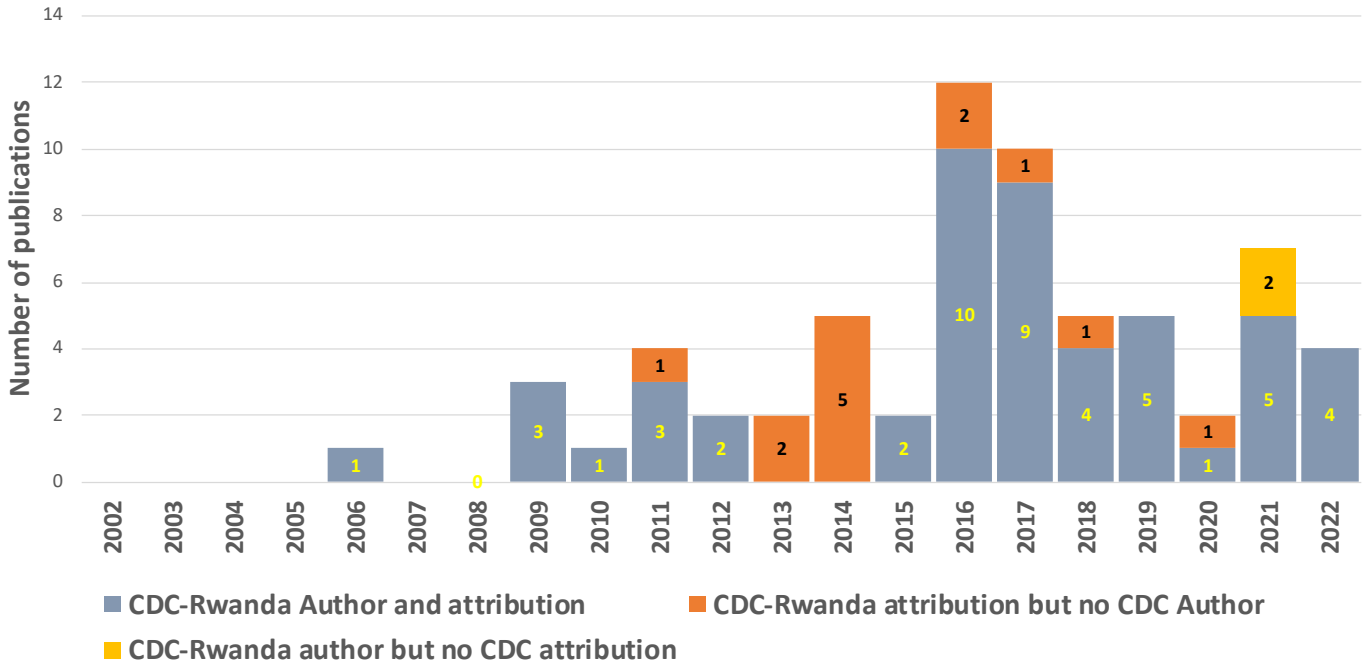
2017
• NCBT recognized as a regional centre of excellence in Blood Transfusion Practice and is awarded the highest – level 3 – international standards accreditation by the Africa Society for Blood Transfusion.

2019
• First large Rwanda Population-based HIV impact assessment conducted with 11,219 households surveyed yielding important HIV Hepatitis B and C information.

2022


• 64 trainees from six cohorts graduated from Rwanda's Advanced FETP program
• 66% of all people living with HIV are enrolled in TB preventive therapy. The TB treatment completion rate is 94%

CDC-funded Scientific Publication Curve



Current trends in Rwanda's HIV/AIDS epidemic

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Objective: To review the trajectory of Rwanda's HIV epidemic, including long term trends and more recent trends in HIV prevalence, markers of HIV incidence, and behavioural indicators.
Methods: This paper reviews the history of HIV serological and behavioural surveillance efforts in Rwanda, dating back to the early 1980s, synthesising findings from surveillance, research, and other relevant HIV programmatic data. The documentation reviewed includes published findings, conference abstracts, and unpublished analyses. Special emphasis is given to more recent sentinel surveillance results and data collected using known, documented methods. Recent trends in HIV prevalence were assessed among sites participating in the three most recent consecutive rounds of antenatal clinic sentinel surveillance.
Results: Early HIV surveillance in Rwanda documented high HIV prevalence in urban areas with HIV widely disseminated into rural areas by 1986. Between 1988 and 1996, HIV prevalence among pregnant women ranged from 21% to 33% in Kigali, from 8% to 22% in other urban settings, and from 2% to 12% in rural settings. More recent surveillance among pregnant women has demonstrated more moderate prevalence, with urban/rural differences narrowing slightly. Between 1998 and 2003, HIV prevalence may have declined in urban areas, whereas rural areas appear to have remained stable. Age at first sexual intercourse is relatively late in Rwanda (20 years for both males and females) and has remained stable since at least 1992.
Conclusions: The present analysis suggests that Rwanda may have experienced declines over the long term in HIV prevalence in urban areas, especially in Kigali, and may have stable or slightly rising HIV prevalence in rural areas. The limited behavioural data available suggest that, on the national level, Rwanda may benefit from a unique combination of low numbers of partners and late sexual debut, which may have had a mitigating effect on HIV prevalence.

Rwanda is a small, landlocked, central African country with a population of 8 162 175,[1] making it Africa's most densely populated country; 83% of the population resides in rural areas. Rwanda was among the first African countries to document AIDS cases in 1983,[2] and subsequent HIV/AIDS surveillance has confirmed that Rwanda's HIV epidemic is longstanding and severe in many settings.

Rwanda's early response to its HIV/AIDS epidemic was relatively rapid and sustained. In 1985, the Ministry of Health and the Red Cross established one of the first and most effective blood donor screening programmes in Africa.[3] In 1986, Rwanda was the first country in the world to conduct and report on a nationally representative HIV seroprevalence survey.[4 5] Also, in 1986, the Ministry of Health, the Red Cross, and the Norwegian Red Cross initiated an extensive AIDS education programme using radio and public health educators.[3] In 1987, the National AIDS Program was established in collaboration with the World Health Organization (WHO).

Rwanda's civil war began in 1990. Between April and July 1994, genocide claimed the lives of an estimated 800 000 Rwandese, displaced nearly 4 million people, and had a devastating impact on national health infrastructure.[6–8] Recent years have been characterised by a dramatic increase in resources to fight the HIV/AIDS epidemic (through the Global Fund, the World Bank, the US government, and others) and a corresponding increase in the availability of services such as voluntary counselling and testing (VCT), prevention of mother-to-child transmission (PMTCT), and antiretroviral therapy (ART). With these resources, the Government of Rwanda has rapidly launched and brought to scale national HIV/AIDS services. VCT services, which first became available in 1997, are now available at 226 sites. PMTCT services began in 1999 and have expanded to 208 sites. Since the introduction of the first ART site in 1999, Rwanda has expanded treatment availability to 83 sites.

In the context of the rapid scale-up of HIV prevention, care, and treatment programmes, it is important to document magnitude and trends in the HIV epidemic. The objective of this paper is to review the trajectory of Rwanda's HIV epidemic, including long term trends and more recent trends in HIV prevalence, markers of HIV incidence, and behavioural indicators.

METHODS

In this paper we review the history of surveillance efforts in Rwanda, dating back to the early 1980s. We have synthesised findings from Rwandan surveillance, research, and other relevant HIV programmatic data, including national and targeted HIV seroprevalence studies, the national sentinel surveillance system, and available behavioural studies. The documentation reviewed includes published findings, conference abstracts, and unpublished analyses. Special emphasis is given to more recent sentinel surveillance results and data collected using documented, internationally accepted methods.

We assessed recent trends in HIV prevalence among sites participating in the three most recent consecutive rounds of antenatal care (ANC) sentinel surveillance. Trends were assessed by site, site setting, age group, and parity with χ^2 tests for linear trend. HIV prevalence among 15–24 year old

Abbreviations: AIDS, acquired immune deficiency syndrome; ANC, antenatal clinic; DHS, Demographic Health Survey; HIV, human immunodeficiency virus; STI, sexually transmitted infection; VCT, voluntary counselling and testing

Table 1 Summary of HIV prevalence at ANC sentinel surveillance sites, Rwanda 1998–2003

	Kigali			Other urban		Rural	
Year	No. of sites	Median prevalence	Range (no. of sites)	Median prevalence	Range (no. of sites)	Median prevalence	Range (no. of sites)
1998	10	16.5	14.7–18.2 (2)	10.2	7.1–13.2 (5)	3.3	2.3–6.2 (3)
2002	24	13.0	13.0–13.0 (2)	6.7	3.7–8.3 (9)	3.0	1.2–5.1 (12)
2003	24	13.2	10.2–16.2 (2)	6.3	3.1–9.3 (9)	2.8	1.2–5.6 (12)

women and among primiparous women was considered as a proxy for HIV incidence.

We defined urban and rural classifications for surveillance sites in accordance with Rwandan government conventions, with the ''other urban'' classification further distinguishing between Kigali and urban areas outside of the capital city.[9]

RESULTS

Rwanda's HIV/AIDS surveillance efforts began in 1984 with the establishment of a national AIDS case reporting system in hospitals and health centres. AIDS case definitions used in Rwanda have changed over time, with the current WHO case definition for AIDS surveillance in use since 1998. Between 1990 and 2002, the system recorded steadily increasing numbers of new AIDS cases with between 1000 and 4000 new case reports per year. This was followed more recently by dramatic increases in cases in 2003 and 2004 (over 6000 and 12 000 cases reported, respectively) as a result of improved reporting and the growing availability of HIV testing, care, and treatment services in Rwanda since 2000 (Ministry of Health, Health Information System, unpublished data, 2004).

The first nationally representative household HIV seroprevalence survey was completed in 1986 using probability proportionate to size cluster sampling. Thirty urban and 30 rural clusters were selected for a total sample size of 2820 individuals. The survey demonstrated substantial urban/rural differences in HIV prevalence, with an estimated urban prevalence of 17.8% and a rural prevalence of 1.3%.[4 5] Peak HIV prevalence was observed in the 26–40 year age group in both urban and rural samples (30.0% and 2.8%, respectively). A national HIV prevalence estimate of approximately 2% was calculated from the study.[5]

In 1997, a more limited household HIV seroprevalence survey was carried out among 30 clusters in each of the catchment areas surrounding five ANC sentinel surveillance sites.[10] A total of 4750 individuals were included in the survey. An overall HIV prevalence of 11.1% was reported from this survey, and little difference was detected between urban and rural prevalence (12.5% and 10.8%, respectively).

Several other HIV seroprevalence studies were carried out in specific groups of interest in Kigali and in other urban settings in Rwanda between 1986 and 1995.[3 11–14] These special studies were not part of the national sentinel surveillance system, but instead were designed to address specific research questions using various methods. Observed HIV prevalence among pregnant women ranged from 9.3% in 1991 in Butare (Rwanda's second largest city) to 32% in 1988 at Kigali's largest hospital. Surveys among commercial sex workers conducted in Butare in 1983 and 1984 documented extremely high HIV prevalence (75% and 88%, respectively).[15]

In 1988, Rwanda established its HIV sentinel surveillance system among ANC attendees and patients with STIs at select sites throughout the country. Leftover specimens from routine clinical services in these settings were anonymously tested for HIV. The first three sentinel surveillance rounds were conducted in 1988, 1991, and 1996. For this period, HIV prevalence in four Kigali sentinel ANC sites ranged from 20.6% to 32.6% (median 25.7%). At four other urban sites outside Kigali, observed prevalence ranged from 8.2% to 21.6% (median 9.9%). At 10 rural sites, prevalence ranged from 2.0% to 12.3% (median 2.6%). During the same years, the sentinel surveillance system also documented high levels of HIV prevalence among STI patients surveyed at a total of five sites over two rounds of surveillance ranging from 23.3% to 65.5% (median 56.5%).[16]

The national sentinel surveillance system was expanded and improved in 2002 to include a total of 24 sentinel ANC sites, with two sites in each of Rwanda's 12 provinces, to approach more representative national coverage. The number of rural sites in the system increased from three to 12, and the number of ''other urban'' sites increased from five to nine. In order to improve precision of prevalence estimates, sample sizes per site were increased in 2002. The average sample size per sentinel site increased from 385 in 1998 to 489 and 484 in 2002 and 2003, respectively. Quality control for serological testing and site supervision were also strengthened.[17]

Table 1 presents a summary of HIV prevalence figures from all sites surveyed during the three most recent rounds of ANC sentinel surveillance. In general, HIV prevalence is consistently highest in the capital Kigali, followed by other urban areas, with more moderate prevalence recorded in rural sites. Between 1998 and 2003, in two Kigali sites observed HIV prevalence ranged from a high of 18.2% in 1998 to 10.2% in 2003.[17 18] HIV prevalence in rural sites was consistent over the six year period at approximately 3%. Kigali and ''other urban'' sites show more variation in HIV prevalence with the 1998 survey registering the highest levels.

Recent trends in HIV prevalence from ANC sites were assessed using only those six sentinel sites that were included in the three most recent rounds of sentinel surveillance. Figure 1 illustrates that prevalence at two rural sites in Kigali Ngali and Kibungo provinces has remained relatively stable, whereas Kigali and ''other urban'' sites (in Kibungo and Byumba provinces) recorded significant declines since 1998. However, in 2002 and 2003 these declines were less evident.

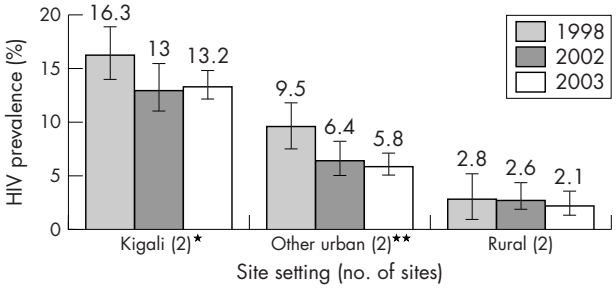

Figure 1 Trends in HIV prevalence by site setting and year of survey, in the six sentinel ANC sites participating in three rounds of surveillance, Rwanda 1998–2003. *χ^2 for trend $p=0.03$ **χ^2 for trend $p<0.01$.

Table 2 HIV prevalence trends at ANC sentinel surveillance sites by site setting, age group, and at first pregnancy, Rwanda 1998–2003

	Kigali				Other urban				Rural			
	1998	2002	2003	p*	1998	2002	2003	p*	1998	2002	2003	p*
15–24	13.1	9.8	10.3	0.09	8.6	5.8	5.0	0.04	2.9	2.0	2.1	0.42
25–34	19.9	15.0	15.4	0.06	11.1	8.0	6.3	0.01	2.4	3.9	2.7	0.54
35–49	16.7	10.7	21.5	0.78	7.5	3.6	6.6	0.50	1.8	0.6	0.7	0.31
First pregnancy	13.3	10.8	8.2	0.05	6.7	4.8	4.8	0.38	3.1	0.5	1.0	0.04

*p value for χ^2 for linear trend.

Trends in individual sites were also considered. Two urban sites (one in Kigali and one in Kibungo) appear to have declining HIV prevalence since 1998, and in both rural sites no trends were evident (data not shown).

In order to discern possible trends in HIV incidence, table 2 presents HIV prevalence by age group and at first pregnancy for each site setting. In Kigali, as well as in "other urban" sites, there is a general decline in prevalence evident in the youngest age group; however, this decline is significant only in the "other urban" site grouping. No clear trends were evident in the youngest age group in rural sites. When considering HIV prevalence levels among women attending ANC for their first pregnancy, significant declines were noted in Kigali sites and in rural sites.

The availability of behavioural data on the population level in Rwanda is limited, and repeated surveys with similar methods and populations have not been conducted. Therefore, assessing trends in behaviours is not currently possible. However, some key behavioural indicators are available from selected surveys. The Demographic Health Survey (DHS) is conducted in Rwanda every five years with a nationally representative sampling scheme described elsewhere.[19 20] The most recent survey conducted in 2000 documents a relatively late sexual debut in Rwanda among both males and females (median age 20.6 and 20.1, respectively), with individuals in urban and rural areas reporting similar age of sexual debut. Between the 1992 and 2000 surveys, the median age of sexual debut among females may have increased slightly from 19.7 to 20.1.[19 20] A large behavioural survey conducted in 2000 among 15–19 year olds in six of Rwanda's 12 provinces showed that 29% of males and 12% of females surveyed reported ever having had sexual intercourse. Another survey conducted in Butare province in 2002 found that among 15–19 year olds, 12.2% of males and 5.6% of females were sexually active.[21]

In the general population, Rwandans report low levels of multiple sexual partnerships. In the 2000 DHS, of all women in a partnership, only 0.6% report more than one sexual partner in the preceding 12 months, and among single women the figure is 0.4%. Of men in partnerships, only 1.8% report more than one sexual partner in the preceding 12 months, and among single men the figure is 1.6%.[20]

Information on condom use is limited and somewhat varied. In the 2000 behavioural survey, 10% of sexually active youth (15–19 years) reported ever having used a condom.[22] In other studies among higher risk groups, condom use is more frequently reported. Reported rates of condom use among commercial sex workers surveyed in 2000 are high, with 81% reporting using a condom at last sex.[23] Among lorry drivers surveyed in 2000, 63% reported condom use at last sex with an occasional partner, and 91% use at last sex with a commercial sex worker.[24]

DISCUSSION

Early surveillance data indicate an explosive HIV/AIDS epidemic in Rwanda, with a high urban prevalence and widely disseminated HIV infection in rural areas of the country by 1986. This is similar to the early course of the epidemic in neighbouring countries.[25]

With the exception of one survey conducted in 1997, urban/rural differences in HIV prevalence have been well documented since 1986 and continue to the present, although the magnitude of these differences appears to have narrowed over time. In 1986, an urban prevalence of 17.8% and a rural prevalence of 1.3% were recorded. Recent sentinel surveillance shows somewhat lower urban prevalence than during the 1980s, and substantially higher rural prevalence on the order of a twofold to threefold increase. This is suggestive of a general trend toward declining prevalence in urban Rwanda, after a peak at some point in the late 1980s or early 1990s, and slowly increasing prevalence in rural Rwanda. There are methodological issues that limit more definitive conclusions from the data. Sites selected for seroprevalence surveys have changed since the 1980s. For example, many key early seroprevalence studies were conducted among pregnant women at the largest reference hospital in Kigali, whereas more recent prevalence data from Kigali come from sentinel health centre sites. It is possible, therefore, that the hospital based studies of the 1980s and early 1990s were conducted among a higher risk group of pregnant women than the more recent surveillance. In addition, prevalence estimates obtained using a population based sample such as the 1986 survey and more recent ANC sentinel surveillance data should be compared cautiously due to the different populations surveyed and different methods used.

The 1997 survey conducted in areas surrounding five ANC sentinel sites did not detect significant differences between urban and rural HIV prevalence. Despite the limited geographical scope of the survey, these results have been interpreted as indicative of national HIV prevalence levels, and have also led to the conclusion that differences in levels of HIV prevalence in urban and rural Rwanda had disappeared in the aftermath of the war. Given the clear urban/rural prevalence differences that continue to be documented through sentinel surveillance, the interpretation of the 1997 survey appears to have been inaccurate; urban areas have markedly higher HIV prevalence than rural areas.

Careful consideration of trends in recent HIV prevalence is important, not only for policy development and programme planning, but also to corroborate the long term trends suggested above. In the past six years, HIV prevalence remains highest in Kigali, with more moderate prevalence in "other urban" and rural settings. There are indications that HIV prevalence and incidence may be decreasing in Kigali, including significant declines among primiparous women and overall prevalence declines since 1998, however, no behavioural trend data or other evidence are available to explain these observations. Rural prevalence shows no signs of decline during this period. These two trends in the short term (urban prevalence possibly declining, with rural trends undetectable) are consistent with the long term trends proposed above. Certain methodological considerations relating to the analysis of recent trends should be noted.

Assessing trends in prevalence is best achieved by comparing rates in the same sentinel sites over time. Rwanda's surveillance system has data from a limited number of years in which the same sites were used, reducing our ability to detect clear trends. Also, the convention of using HIV prevalence among the youngest women as a proxy for HIV incidence is known to provide only a general indication of true incidence. In Rwanda, late sexual debut among women makes analysis of the 15–19 year age group more difficult, due to a low number of pregnant women in the youngest age groups. The incidence analysis therefore considered both the 15–24 year age group and primiparous women as indicators of potential new infections.[26]

National HIV prevalence estimates have varied widely over the past decade, and have been revised downward during that time. The Joint United Nations Programme on AIDS (UNAIDS) national estimates for Rwanda have declined from 12.8% in 1998 to 5.2% in 2004.[27 28] The most recent revised prevalence estimates by the Rwandan Ministry of Health are consistent with the current UNAIDS estimate and present an upper limit for rural prevalence of 4% and an upper limit for urban prevalence of 11%.[29] Although some of the changes may reflect actual declining prevalence, an important part of the change is likely due to improvements in surveillance methodology over time, specifically increased coverage of sentinel sites outside of Kigali, especially in rural areas of the country, where relatively lower prevalence has been measured. The massive mortality and displacement of the Rwandan population during and after the 1994 war are likely to have influenced HIV prevalence patterns in the country during this period, although the magnitude and direction of these changes cannot be discerned from available data.

Given the limited behavioural data available in Rwanda, it is difficult to speculate on changes in sexual behaviour over time. However, Rwanda's relatively late and stable sexual debut figures and the infrequency of multiple sex partners are well documented in two nationally representative DHS surveys, and sexual behaviour information from smaller surveys among youth is consistent with late sexual debut. These data describe a somewhat unique and potentially protective environment against a more explosive spread of HIV on a population level, and may have allowed Rwanda to avoid reaching sustained national prevalence at a much higher level than it apparently has. Kigali presents an exception to this national picture: higher risk sexual behaviour in Rwanda's only major city is consistent with the markedly higher HIV prevalence observed there. Similarly, condom use among some urban high risk groups, such as lorry drivers and commercial sex workers, was relatively high in 2000, and may be contributing to slowing the spread of HIV.

SUMMARY AND FUTURE DIRECTIONS

In spite of the acknowledged limitations of available data, the present analysis suggests that Rwanda may have experienced declines over the long term in HIV prevalence in urban areas, especially in Kigali, and may have stable or rising HIV prevalence in rural areas. In recent years, Rwanda's surveillance system has been significantly strengthened and is well positioned to provide more conclusive data in the near future. The expanded HIV sentinel surveillance system will continue in 2005 in at least 24 sites, providing critical new information on recent trends. Rwanda is currently conducting its second nationally representative household HIV seroprevalence survey (RDHS+), which will provide national and regional HIV prevalence estimates, and which will allow for adjustments to national estimates derived from ANC sentinel surveillance. Rwanda also plans to conduct HIV incidence studies using new serological methods to measure more accurately absolute levels of recent HIV infections and emerging trends in incidence.

Key message

Rwanda's surveillance data demonstrate clear differences in HIV prevalence between urban and rural settings, with urban areas more seriously affected, especially the capital, Kigali. There is growing evidence that HIV prevalence is declining in urban areas in Rwanda.

CONTRIBUTIONS OF AUTHORS

E Kayirangwa and A Kabeja lead the Epidemiology Unit at the Treatment and Research AIDS Center and have managed all aspects of the ANC sentinel surveillance system since 2001. L Munyakazi, Director of the Treatment and Research AIDS Center, supervised surveillance efforts and provided review and interpretation of the data. J Hanson has provided technical assistance to the Treatment and Research AIDS Center in conducting HIV surveillance since 2001. The paper was prepared primarily by E Kayirangwa and J Hanson.

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Competing interests: none declared

The findings and conclusions in this manuscript are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

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Comparing two service delivery models for the prevention of mother-to-child transmission (PMTCT) of HIV during transition from single-dose nevirapine to multi-drug antiretroviral regimens

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Abstract

Background: Mother-to-child transmission (MTCT) of HIV has been eliminated from the developed world with the introduction of multi-drug antiretroviral (md-ARV) regimens for the prevention of MTCT (PMTCT); but remains the major cause of HIV infection among sub-Saharan African children. This study compares two service delivery models of PMTCT interventions and documents the lessons learned and the challenges encountered during the transition from single-dose nevirapine (sd-nvp) to md-ARV regimens in a resource-limited setting.

Methods: Program data collected from 32 clinical sites was used to describe trends and compare the performance (uptake of HIV testing, CD4 screening and ARV regimens initiated during pregnancy) of sites providing PMTCT as a stand-alone service (*stand-alone site*) versus sites providing PMTCT as well as antiretroviral therapy (ART) (*full package site*). CD4 cell count screening, enrolment into ART services and the initiation of md-ARV regimens during pregnancy, including dual (zidovudine [AZT] +sd-nvp) prophylaxis and highly active antiretroviral therapy (HAART) were analysed.

Results: From July 2006 to December 2008, 1,622 pregnant women tested HIV positive (HIV+) during antenatal care (ANC). CD4 cell count screening during pregnancy increased from 60% to 70%, and the initiation of md-ARV regimens increased from 35.5% to 97% during this period. In 2008, women attending ANC at *full package* sites were 30% more likely to undergo CD4 cell count assessment during pregnancy than women attending *stand-alone* sites (relative risk (RR) = 1.3; 95% confidence interval (CI): 1.1-1.4). Enrolment of HIV+ pregnant women in ART services was almost twice as likely at *full package* sites than at *stand-alone* sites (RR = 1.9; 95% CI: 1.5-2.3). However, no significant differences were detected between the two models of care in providing md-ARV (RR = 0.9; 95% CI: 0.9-1.0).

Conclusions: All sites successfully transitioned from sd-nvp to md-ARV regimens for PMTCT. *Full package* sites offer the most efficient model for providing immunological assessment and enrolment into care and treatment of HIV+ pregnant women. Strengthening the capacity of *stand-alone* PMTCT sites to achieve the same objectives is paramount.

Background

Mother-to-child transmission (MTCT) of HIV remains the major route of pediatric HIV infection in sub-Saharan Africa, where over 90% of the 2.1 million children living with HIV reside [1-3]. Since 2000, modest progress has been made towards expanding access to prevention of MTCT (PMTCT) services in sub-Saharan Africa. While access to HIV testing during pregnancy has improved, most PMTCT programs still rely on administration of single-dose nevirapine (sd-nvp) to mothers and babies, a simple, inexpensive, but low efficacy antiretroviral (ARV) regimen to reduce the risk of HIV transmission [3,4]. Since 2004, the World Health

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Organization (WHO) guidelines have recommended the use of more efficacious multidrug antiretroviral (md-ARV) regimens for PMTCT, including highly active antiretroviral therapy (HAART) for women with advanced disease and short course dual prophylaxis for healthier women not yet eligible for treatment [5]. In November 2009, the WHO issued revised guidelines emphasizing the use of md-ARV for PMTCT as well as the critical need for measuring antenatal CD4 cell counts to determine HAART eligibility [6]. However, only 12% and 28% of HIV+ pregnant women in PMTCT programs received CD4 cell count assessments in 2007 and 2008, respectively, in low- and middle-income countries [1,7]. Moreover, the provision of HAART in antenatal care (ANC) is a challenge due to maternal and child health (MCH) staff shortages, the reliance on medical doctors for HAART initiation and the weak linkages between PMTCT and antiretroviral therapy (ART) services, which often preclude women from being fast-tracked into HIV care and treatment programs [8-11]. Although many sub-Saharan African countries have introduced md-ARV for PMTCT, little has been documented about these experiences [10-13].

Rwanda has a generalized HIV epidemic, 3.6% of women aged 15-49 are living with HIV according to the Demographic and Health Survey conducted in 2005 [14]. It is estimated that approximately 7,700 newborns are at risk of acquiring HIV each year [15]. A national PMTCT program was launched in 1999-2000 at three pilot sites,[16] and coverage expanded to 285 sites nationwide by the end of 2007 [17]. In September 2005, the national PMTCT guidelines were revised to reflect the WHO recommendations that included more effective md-ARV regimens [17]. This study compares two service delivery models for the PMTCT of HIV and compares the uptake of HIV testing, CD4 screening and ARV regimens initiated during pregnancy between 2007 and 2008. It also documents the success of implementation of the program and the challenges encountered during the transition from sd-nvp to md-ARV regimens for PMTCT in 32 sites in Rwanda between July 2006 and December 2008.

Methods

Program description

Since 2004, the International Center for AIDS Care and Treatment programs (ICAP) of Columbia University, Mailman School of Public Health (NY, USA), supports the implementation of HIV prevention, care and treatment programs in Rwanda including capacity building of staff, on-site mentoring, renovation of infrastructure, provision of equipment including laboratory machines, technical support to monitoring and evaluation, and operational research. In July 2006, ICAP supported the implementation of PMTCT programs at five health facilities (sites), including four district hospitals (DHs) and one health center (HC), and expanded to 32 sites (four DHs and 28 HCs) by December 2008 in the Western Province (Kibuye and Gisenyi regions) and Kigali, the capital city.

PMTCT services are routinely implemented within MCH services in Rwanda. Opt-out HIV counseling and testing (CT) is routinely provided in the ANC by trained nurses using sequential rapid HIV tests following the national algorithm, with results available the same-day [18]. Partner testing and couple CT is strongly promoted during pregnancy. The ARV regimens recommended for PMTCT are summarized in Figure 1 [19]. WHO clinical staging and CD4 cell count assessment is recommended for all HIV-infected pregnant women. PMTCT staff were trained and mentored to assess the clinical stage and interpret the CD4 cell count test results. At the time of writing this report, the prescription of HAART for eligible patients was still limited to trained physicians, mostly working in ART clinics at district or referral hospitals, and could not be initiated by nurses working in PMTCT programs, predominantly at the HC level.

Two models of PMTCT service delivery were defined: *"full package"* sites where PMTCT and ART services were both located on the same premises and *"stand-alone"* sites where only PMTCT services were available on-site. *Full package* and *stand-alone* sites were authorized to provide md-ARV regimens to pregnant women. However, at the time of writing this report, both *stand-alone* and *full package* sites were providing dual ARV and the sd-NVP regimens, but only *full package* sites offered 'therapeutic' HAART and 'short-course' HAART

Scenario 1: HIV-infected pregnant women are considered medically eligible for lifelong 'therapeutic' HAART (t-HAART) if they have WHO clinical stage 4 disease or a CD4 cell count < 350 cells/mm^3. Recommended regimens: zidovudine (AZT) or stavudine (d4T) + lamivudine (3TC) + nevirapine (NVP).

Scenario 2: Women who present late (> 34 weeks of gestation) are eligible for 'short-course' HAART (sc-HAART), irrespective of the WHO staging or CD4 cell count. After delivery, HAART is discontinued if the CD4 cell count > 350 cells/mm^3 (with a one-week AZT/3TC tail) or continued for life if CD4 cell count < 350 cells/mm^3. Recommended regimen: AZT or d4T + 3TC + NVP.

Scenario 3: Women, not eligible for HAART, receive short-course AZT (sc-AZT) after 28 weeks of gestation, plus SD-NVP at the onset of labor, with a one-week AZT/3TC tail.

Scenario 4: HIV-negative pregnant women in discordant couples with a HIV-infected partner, as well as pregnant women testing HIV positive in the labor room, receive single dose NVP (sd-NVP in labor with a one-week AZT/3TC tail.

Scenario 5: Women receiving HAART at the time of conception continue treatment. Efavirenz should be avoided in the first trimester.

All babies of HIV positive mothers receive SD-NVP at birth (within 72 hours) plus four weeks of AZT syrup.

Figure 1 Guidelines for antiretroviral regimens for the prevention of mother-to-child transmission of HIV in Rwanda, September 2005.

(Figure 1). Women eligible for HAART in *full package* sites were initiated as soon as possible during pregnancy by the ART physician, whereas *stand-alone* sites referred HAART-eligible women to the nearest ART site for enrolment into ART services and the initiation of treatment.

Immunologic assessment during pregnancy

In 2006, of the five PMTCT sites, only one had the equipment required to measure CD4 cell counts (FACS-Count [Becton Dickinson, San Jose, CA, USA]), the other four sites processed CD4 samples at the nearest laboratory possessing the necessary equipment. CD4 testing requisition was initially only performed for patients within ART clinics since a unique patient identifier (TRACnet number), only provided in the ART clinic, was required by the lab technician before blood could be taken. All pregnant women identified in PMTCT had to be referred to the ART clinic, within the same premises or via a referral (for *stand-alone* sites), to receive a TRACnet ID prior to CD4 testing requisition. In addition, because most CD4 blood samples originated from patients in ART services, pregnant women were therefore asked to come back on a different day, generally within a week after receipt of an HIV positive test result, as this allowed for common batching of blood samples from patients in ART services.

Between 2007 and 2008, DH supervisors teamed with mentors from ICAP to support health facilities in assessing and addressing the barriers (Figure 2) to immunologic assessment using an approach described elsewhere [20]. Figure 2 summarizes the changes recommended and gradually implemented at district and site levels.

Capacity building for the delivering of multidrug ARV (md-ARV) regimens initiation during pregnancy

In 2006, few nurses were trained to administer md-ARV regimens for PMTCT. Refresher training and practical sessions were organized and 297 staff were trained or retrained in 32 sites during the period under review. In each district, the site support staff members worked with district health teams to provide regular on-site

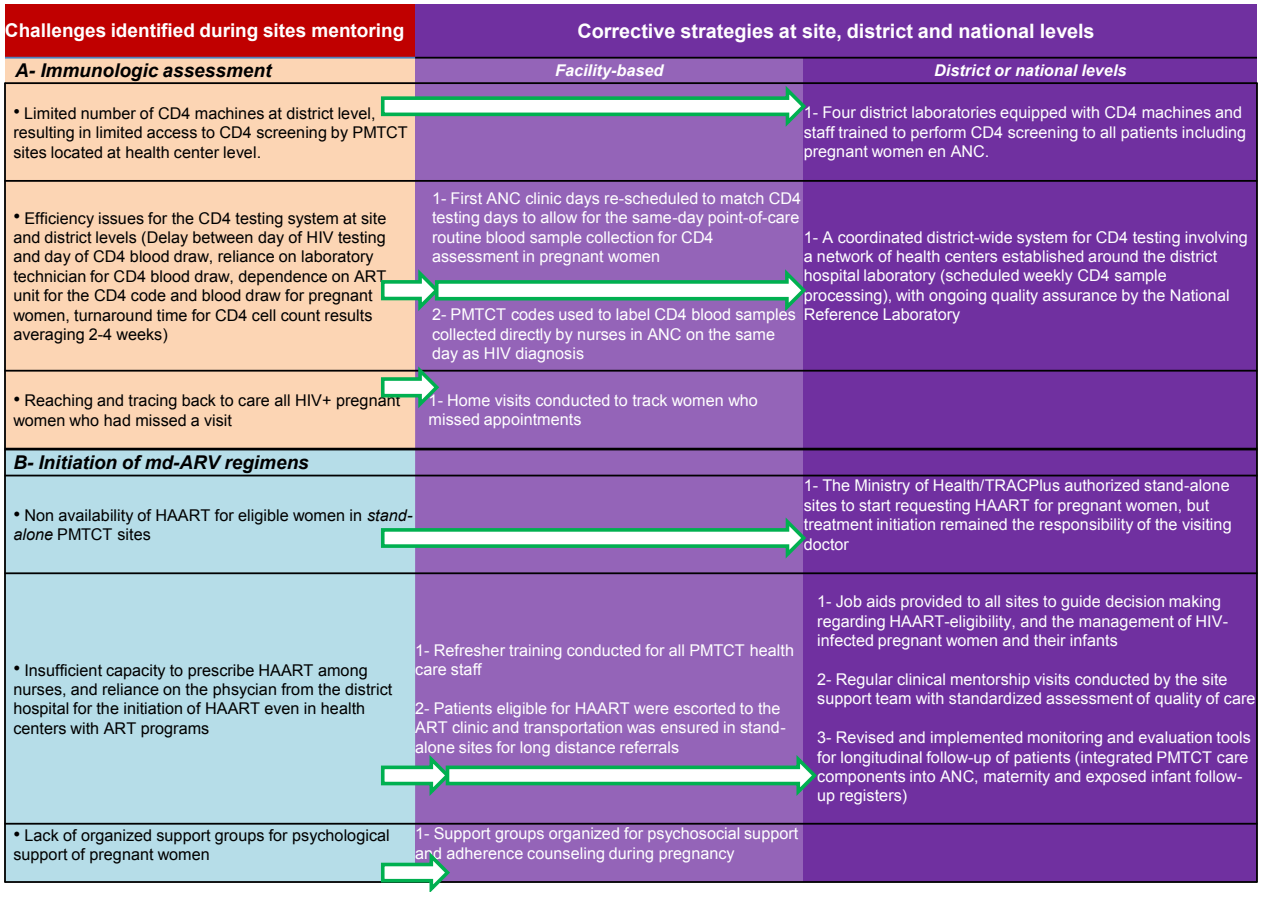

Figure 2 Challenges and corrective strategies for improving immunologic assessment and initiation of md-ARV regimens during pregnancy.

mentoring following the completion of formal didactic training.

Data collection and statistical analysis

We collected the following routine PMTCT program indicators from the program monitoring database for the period July 2006 through December 2008: *number of pregnant women attending first ANC, number of women known to be HIV positive at first ANC, number of women tested for HIV, number of women tested HIV positive, number of male partner counseled and tested for HIV, number of HIV positive women assessed for CD4 cell count during pregnancy, number of women who received CD4 cell count results, number of women with CD4 cell counts < 350 cells/mm3, number of HIV positive women enrolled into HIV care and treatment, number of women with CD4 cell counts < 350 cells/mm3 who initiated HAART for life 'therapeutic' HAART (t-HAART) during pregnancy, number of women who initiated short-course HAART (sc-HAART) for prophylaxis during pregnancy, number of women who initiated dual ARV (AZT/NVP) prophylaxis during pregnancy, number of women who received sd-nvp only (sd-NVP) for PMTCT prophylaxis during pregnancy*. These indicators are routinely collected from site registers, and reported monthly to district health offices for compilation and transmission to the central level. In January 2007, the national program revised the PMTCT program monitoring tools, including registers and monthly summary forms, adding new indicators for CD4 cell count assessments and enrolment in HIV care and treatment programs and HAART initiation. We reported changes over time for each indicator, and using chi-square tests of association with two-sided p-values, we compared the performance of the program across each indicator for the period 2007 - 2008, when comprehensive PMTCT program data was available.

Finally, we compared the two model of service delivery (*full package* vs. *stand-alone*) across key program indicators using relative risks (RR) with associated 95% confidence intervals (CI) for the year 2008 only. The aggregated format of our data did not allow for controlling the effect of clustering across sites. In our analysis, we defined the following ARV regimens options as "more efficacious" ARV regimens (dual ARV, HAART for life, and sc-HAART). Data analysis was conducted using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA). The data used for this analysis were aggregated site level indicators routinely collected by the national PMTCT program, and therefore did not contain any patient identifier. This secondary data analysis received approval from the Columbia University Institutional Review Board (IRB) and was also granted the non-research status (exempted from ethical review) by the Centers for Disease Control and Prevention (CDC), Atlanta, USA.

Results

HIV testing uptake among pregnant women and male partners

Between July 2006 and December 2008, 40,674 pregnant women made a first visit to an ANC and were counseled for HIV; 99% accepted HIV testing and 4% tested HIV+; 67% male partners also received HIV testing (Table 1). HIV testing rates, already extremely high at the start of reporting in 2006, increased from 98% to 99% ($p < 0.001$) from 2007 to 2008. Partner testing rates also increased from 57% in 2007 to 75% in 2008 ($p < 0.0001$).

Immunologic assessment and enrolment in ART services during pregnancy

Overall, 69% of 2,048 HIV+ (known and newly identified HIV+) pregnant women were screened for their CD4 cell count during pregnancy, with the proportion increasing from 60% in 2006 to 70% in 2007 and 2008. Additional indicators collected in 2007-2008 showed that 96% of 1,268 women assessed for their CD4 cell count returned to the health facility to retrieve their results and 54% of 1,381 HIV+ women identified from July 2007 through December 2008 were enrolled in ART services. CD4 cell count screening remained at 70% in 2007 and 2008 ($p = 0.18$), however, the percentage of women receiving their CD4 test results and enrolling in HIV care and treatment programs increased significantly, from 92-98% ($p < 0.001$) and 41-60% ($p = 0.04$), respectively (Table 1).

ARV regimens initiated during pregnancy

Between July 2006 and December 2008, 71% of HIV+ pregnant women received an ARV regimen for PMTCT. The proportion of HIV+ pregnant women initiating more efficacious md-ARV regimens increased from 35.5% in 2006 to 97% in 2008 and women receiving sd-nvp decreased from 64.5% to 3% during the same time-period (Table 1). A total of 292 (24%) women were eligible for HAART in 2007-2008 based on the Rwandan national guidelines (CD4 < 350 cells/mm^3), and 83% initiated HAART during pregnancy. The proportion of eligible women initiating HAART declined slightly from 86% in 2007 to 79% in 2008 ($p = 0.12$).

Comparing the models (*full package* vs. *stand-alone site)* of service delivery

By December 2006, 37.5% of PMTCT sites were providing the *full package* service and 62.5% were *stand-alone* sites; the proportion of *full package* sites increased to

Table 1 HIV testing, CD4 cell count assessment, and ARV regimens initiated during pregnancy in Rwanda, from July 2006 through to December 2008 (N= 32 sites)

	2006 (Jul-Dec) N (%)	2007 N (%)	2008 N (%)	Total N (%)	*p*** *(2007 vs. 2008)*
Total number of sites	14	19	32	-	-
Full package	5 (35.7%)	15 (79%)	18 (56%)	-	-
Counseling and testing of pregnant women in ANC:					
First ANC visit	4,520	15,469	20,685	40,674	-
Known to be HIV positive	NA	135 (0.9%)	291 (1.4%)	426 (1%)	-
Tested for HIV	4,452 (98%)	15,231 (98%)	20,564 (99%)	40,247 (99%)	<0.0001
Tested HIV positive	234 (5%)	741 (5%)	647 (3%)	1,622 (4%)	<0.0001
Partner counseling and HIV testing	NA	8,652 (57%)	15,463 (75%)	24,115 (67%)[$]	<0.0001
CD4 cell count assessment during pregnancy					
Total HIV positive in ANC	234	876	938	2,048	-
Screened for CD4 cell counts[¶]	140 (60%)	610 (70%)	658 (70%)	1,408 (69%)	0.81
Received CD4 cell count results[¶¶]	NA	564 (92%)	647 (98%)	1,211 (96%)[$]	<0.0001
CD4 cell counts < 350 cells/mm^3	NA	132 (23%)	160 (25%)	292 (24%)[$]	0.59
Enrolment of HIV positive women into care and treatment	NA	180/443 (41%)[@]	564/938 (60%)	744/1381 (54%)[$]	-
HAART initiation for women with CD4 cell counts < 350 cells/mm^3	NA	114/132 (86%)	127/160 (79%)	241/292 (83%)[$]	0.12
Total HIV positive in ANC	234	876	938	2,048	
All ARV regimens initiated during pregnancy	155 (66%)	667 (76%)	638 (68%)	1460 (71%)	
Dual (AZT/NVP) prophylaxis	55 (35.5%)	386 (58%)	403 (63%)	844 (58%)	
HAART for life	NA	114 (17%)	127 (20%)	241 (16%)	
sd-nvp *only*	100 (64.5%)	34 (5%)	21 (3%)	155 (11%)	
Short-course HAART	NA	133 (20%)	87 (14%)	220 (15%)	
More efficacious ARV regimens (dual ARV, or HAART for life or sc-HAART)	55 (35.5%)	633 (95%)	617 (97%)	1325 (89%)	

[$] Percentage calculated based on 2007 and 2008 data only.

NA indicates data not available or not routinely reported in the program monthly report.

[¶] Indicates the number of HIV+ pregnant women giving blood for CD4 testing and includes women of known HIV+ status.

[¶¶] Indicates the number of HIV+ women receiving CD4 results in a given period and might include women screened in a previous time period. This number is used as a denominator to compute the proportion of women with CD4 cell counts < 350 cells/mm^3, which reflects the number of women whose results were available and who returned for enrolment in health regimens and subsequent HAART initiation.

79% by 2007, but decreased to 56% by December 2008 with the opening of new PMTCT sites (Table 1).

From January through December 2008, CD4 assessment of HIV+ pregnant women differed across the models of service delivery with women attending *full package* sites 30% more likely to undergo CD4 cell count assessment than women attending *stand-alone* sites [RR = 1.3; 95% CI: 1.1-1.4] (Table 2). Enrolment of HIV+ pregnant women into ART services was almost twice as likely at *full package* sites than *stand-alone* sites [RR = 1.9; 95% CI: 1.5-2.3]. However, no differences were detected between the two sites, *full package* and *stand-alone*, in initiating treatment for eligible women determined to be eligible for HAART [RR = 0.9; 95% CI: 0.7-1.1]) and providing more efficacious ARV regimens [RR = 0.9; 95% CI: 0.9-1.0].

Discussion

Until recently, most PMTCT programs still relied on the administration of sd-nvp to mothers and babies but md-ARV regimens have now been implemented. This report documents the successful implementation of md-ARV regimens, including HAART, for HIV+ pregnant women with advanced disease in 32 PMTCT sites in Rwanda. The transition from sd-nvp to more efficacious regimens occurred independently of the model of service delivery (*full package* vs. *stand-alone*) within a 30-month period. To our knowledge, this is one of the first reports to comprehensively document the transition from a traditional sd-nvp regimen to more effective ARV regimens for PMTCT in a resource-limited setting. Despite PMTCT service decentralization to health centers with limited resources and capacities, addressing health

Table 2 CD4 cell count assessment, enrolment into care and treatment and ARV initiated during pregnancy among HIV positive women according to the type of HIV services package, Rwanda, from January through December 2008

	Full package[$]	Stand-alone	*RR (95% CI)*[#]
Sites, N (%)	18 (56%)	14 (44%)	-
Total HIV positive pregnant women (N)	743	195	-
CD4 cell count assessment, N (%):			
Screened for CD4 cell counts[¶]	547 (74%)	111 (57%)	**1.3 (1.1 - 1.4)**
Received CD4 cell count result[¶¶]	536 (98%)	111 (100%)	0.97 (0.96 - 1.0)
CD4 cell count < 350 cells/mm^3	134 (25%)	26 (23%)	-
Enrolment into care and treatment, N (%)	495 (67%)	69 (35%)	**1.9 (1.5 - 2.3)**
HAART initiation among women with CD4 cell counts < 350 cells/mm^3, N (%)	105 (78%)	22 (85%)	0.9 (0.7 - 1.1)
Received PMTCT prophylaxis or more efficacious ARV regimens:	511 (96%)	106 (100%)	0.9 (0.9 - 1.0)
Dual (AZT/sd-nvp) prophylaxis	331 (62%)	72 (68%)	-
HAART for life	105 (20%)	22 (21%)	-
Short-course HAART	75 (14%)	12 (11%)	-
sd-nvp *only*	21 (4%)	0 (0%)	-

[$] Full package sites provide comprehensive PMTCT and on-site ART services.

[¶] The number of HIV+ pregnant women who underwent the CD4 test, including women tested in ANC and those of known HIV+ status who had not initiated HAART before their current pregnancy.

[¶¶] The number of HIV+ women receiving CD4 results in a given quarter, including all women who received their results at a follow-up visit during the quarter. This number includes women tested in previous quarters who retrieved their CD4 counts during the indicated quarter.

[#] Relative Risk (RR) comparing the full package service (PMTCT and ART) as a reference to the stand-alone service; CI: confidence interval.

systems bottlenecks at site and district levels led to increased numbers of HIV+ women undergoing an immunologic assessment during pregnancy, and improved identification of pregnant women who were eligible for therapy and subsequently initiated on HAART in both *full package* and *stand-alone* sites. However, more effort is needed to ensure effective CD4+ cell count assessments and the enrolment of HIV+ women in ART services in *stand-alone* sites. The finding of such studies will be useful in the design of strategies for implementing the 2009 WHO recommendations into national PMTCT programs.

The number of HIV+ pregnant women who were screened for CD4 cell counts during pregnancy (up to 70% in 2008) and who received their results (up to 98% in 2008) significantly increased following the introduction of changes to the CD4 testing system at both the site and district levels. One major innovation was the same-day point-of-care blood sample taken from HIV+ pregnant women in ANC clinics. The importance of same-day CD4 cell count testing was also highlighted in two studies from South Africa reporting an uptake rate of over 97% for CD4 cell count screening during pregnancy [10,11]. Although most sites in this program sent samples to off-site laboratories mainly at the DH level for CD4 measurement, it could be anticipated that with the implementation of a weekly sample processing system, the turnaround time for CD4 cell count results would be reduced. Our data further suggested that despite the improvements in CD4 cell count assessments over time, women in *full package* sites were more likely to undergo immunologic screening than those in *stand-alone* sites. Although our study did not investigate the reasons for such a difference, it could be hypothesized that in 2008 the addition of 13 new *stand-alone* sites, which likely possessed ineffective CD4 testing systems, reduced the overall performance of *stand-alone* sites.

We found that approximately one quarter of pregnant women were eligible for HAART, based on CD4 cell counts ≤ 350 cells/mm^3. This is two-fold lower than the 55% reported in a study in the Western Cape, South Africa,[11] suggesting that most pregnant women are diagnosed earlier in the course of HIV infection in our clinical settings. In addition, in our findings, a high proportion (85%) of eligible pregnant women initiated HAART with no significant differences between the models of service delivery. Although women in *full package* sites were more likely to undergo CD4 testing, women who received testing and were determined to be eligible were just as likely to initiate HAART in *stand-alone* sites as in *full package* sites in 2008, suggesting that the changes that were introduced had a positive impact, as summarized in Figure 2.

In our report, the uptake of HAART among women identified as eligible was found to be higher than the 51% reported in five sites in the Western Cape [11] and the 75% reported in Gauteng province, [10] South Africa. Similar to the findings in the Western Cape, our study revealed that the model of service delivery did not

influence the rate of HAART initiation during pregnancy [11]. The high uptake of HAART among eligible women identified in our study might be attributable to a number of innovations including improved psychosocial support, escorting eligible women to the ART clinic and liaising with social workers to track women who missed appointments. A tracking system for pregnant women was deemed more feasible in our setting given the small number of HAART-eligible women compared with a higher prevalence setting like South Africa. Furthermore, denial and fear of disclosure to sexual partners was reported as a limiting factor for effective treatment in South Africa, whereas the high rate of partner testing and the roll-out of psychosocial support structures (e.g., associations of people living with HIV and AIDS, and support groups for HIV+ patients) over the past two years could have mitigated the impact of this factor in our setting. Finally, according to the 2008 Rwanda Interim Demographic and Health (I-DHS) survey, about 96% of pregnant women attend at least one ANC visit during their pregnancy; most of them attending ANC for the first time before the end of the second trimester, giving enough time for those women tested HIV infected to start the ARV prophylaxis or treatment.

Health care providers in *full package* sites may be prompted to actively enroll women found to be eligible for HAART in the ART program, given that HAART initiation could be done in the same facility. We could hypothesize therefore, that making HAART available in *stand-alone* sites and accessible for eligible pregnant women may provide a motivation for providers to undertake CD4 cell count screening and enroll HIV+ and eligible pregnant women into ART services. By doing so, it would further reduce the burden on pregnant women who were asked to travel, in some cases, long distances to reach the nearest ART site.

We noted, however, that the two models of service delivery did not differ with regard to HAART initiation among eligible pregnant women. This results from the effective system for referral of eligible pregnant women from *stand-alone* sites to the nearest *full package* site, coupled with the availability of doctors from the DH who usually visit *full package* sites on a weekly basis for HAART initiation among new HIV+ patients. As PMTCT services continue to be scaled-up at the district level, the *"flying doctors"* approach might not be cost-effective and sustainable in resource limited settings. Task-shifting HAART initiation to nurses is therefore necessary and this has been successful performed in various settings [21-24]. Rwanda adopted in 2009 a national policy on task-shifting for HIV services and its implementation will contribute to improve and sustain the timely initiation of HAART, particularly among eligible HIV+ pregnant women.

Some key factors for an effective transition from sd-nvp to md-ARV regimens include among others the capacity building and regular mentoring of nurses, the routine assessment of the quality of care provided by nurses during the transition to md-ARV regimens, the full integration of PMTCT care components into MCH services, the strengthening of the CD4 testing capacity at district level, the reorganizing of services at site level with an emphasis on effective linkages between PMTCT and ART services, and the high level commitment and leadership of the Rwandan government's to improving maternal and child survival, including virtual elimination of pediatric HIV infection.

The analysis carried out in this study was subject to some limitations. A recent analysis of routine PMTCT data in South Africa concluded that there were major weaknesses in the completeness and accuracy of this data which precluded its use in the tracking of process performance of facilities,[25] however, we believe that the routine PMTCT data in Rwanda is of good quality due to the implementation of a rigorous quality assurance process whereby aggregate reports are verified against program registers each month by site support staff. In addition, by focusing the analysis on antenatal services, findings are limited to the initiation of PMTCT regimens during pregnancy, and do not address maternal adherence to ARV regimens during pregnancy, maternal and infant ARV uptake at delivery, or the overall impact of PMTCT interventions on maternal and child health. Also, the improvements introduced in the routine data collection system in 2007 have likely increased reporting on the uptake of various PMTCT interventions, compared with 2006. We were unable to account for clustering of patients within clinics in our analysis, thus underestimating the variance associated with each program indicator. Finally, since several interventions occurred simultaneously, it is difficult to determine the relative importance of each intervention on program performance.

Conclusions

This report has demonstrated that regardless of the model of PMTCT service delivery, it is feasible to transition from sd-nvp regimen to more effective md-ARV regimen in a resource limited, public sector PMTCT program. However, more efforts are needed to ensure effective CD4+ cell count assessment and the enrolment of HIV+ women in ART services in *stand-alone sites*, and task-shifting is necessary to ensure the timely initiation and follow-up of HAART among pregnant women. These findings provide valuable insight which can be applied to the design of effective service delivery models for the transition from sd-nvp to md-ARV within national PMTCT programs in resource limited settings,

accelerating progress towards virtual elimination of MTCT of HIV by 2015 [26].

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Authors' contributions
LT, FT, RC, VM, GT, EM, SK, PM, EK, RS, EJA contributed to the design of the program and the development of the concept for this manuscript. LT, FT, RC wrote the first draft of the manuscript. SK reviewed the laboratory section of the methodology. LT, RC, FT, EJA conducted data analysis and interpretation. And all the authors reviewed the final manuscript.

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Competing interests
The authors declare that they have no competing interests.

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RESEARCH ARTICLE Open Access

Evaluation of the Rapid Scale-up of Collaborative TB/HIV Activities in TB Facilities in Rwanda, 2005-2009

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Abstract

Background: In 2005, Rwanda drafted a national TB/HIV policy and began scaling-up collaborative TB/HIV activities. Prior to the scale-up, we evaluated existing TB/HIV practices, possible barriers to policy and programmatic implementation, and patient treatment outcomes. We then used our evaluation data as a baseline for evaluating the national scale-up of collaborative TB/HIV activities from 2005 through 2009.

Methods: Our baseline evaluation included a cross-sectional evaluation of 23/161 TB clinics. We conducted structured interviews with patients and clinic staff and reviewed TB registers and patient records to assess HIV testing practices, provision of HIV care and treatment for people with TB that tested positive for HIV, and patients' TB treatment outcomes. Following our baseline evaluation, we used nationally representative TB/HIV surveillance data to monitor the scale-up of collaborative TB/HIV activities

Results: Of 207 patients interviewed, 76% were offered HIV testing, 99% accepted, and 49% reported positive test results. Of 40 staff interviewed, 68% reported offering HIV testing to >50% of patients. From 2005-2009, scaled-up TB/HIV activities resulted in increased HIV testing of patients with TB (69% to 97%) and provision of cotrimoxazole (15% to 92%) and antiretroviral therapy (13% to 49%) for patients with TB disease and HIV infection (TB/HIV). The risk of death among patients with TB/HIV relative to patients with TB not infected with HIV declined from 2005 (RR = 6.1, 95%CI 2.6, 14.0) to 2007 (RR = 1.8, 95%CI 1.68, 1.94).

Conclusions: Our baseline evaluation highlighted that staff and patients were receptive to HIV testing. However, expanded access to testing, care, and treatment was needed based on the proportion of patients with TB having unknown HIV status and the high rate of HIV infection and poorer TB treatment outcomes for patients with TB/HIV. Following our evaluation, scale-up of TB/HIV services resulted in almost all patients with TB knowing their HIV status. Scale-up also resulted in dramatic increases in the uptake of lifesaving HIV care and treatment coinciding with a decline in the risk of death among patients with TB/HIV.

Background

Tuberculosis (TB) is a treatable disease but remains the leading cause of death among persons living with HIV/AIDS (PLHIV) [1]. In some settings, up to 50% of patients with both TB disease and HIV infection die during TB treatment with most deaths occurring within 2 months of being diagnosed with TB [2-6]. In 2004, the World Health Organization (WHO) issued policy guidance on collaborative TB/HIV activities to reduce the burden of TB and HIV [7]. The interim policy recommended routine HIV testing for patients with TB disease and ensuring linkages to HIV care and treatment for patients with TB disease diagnosed with HIV infection (hereafter patients with both TB disease and HIV infection will be referred to as patients with TB/HIV). Also in 2004, WHO and UNAIDS issued a joint policy statement recommending routine provider-initiated HIV testing and counseling (PITC) for all patients with TB [8]. The policy recommendations were intended to increase the uptake of HIV testing among patients with TB by shifting from a model of people voluntarily seeking HIV counseling and testing (VCT) to providers initiating HIV testing

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and counseling (PITC). The shift from VCT to PITC resulted in TB clinics serving as points of entry for scale-up of HIV care and treatment services.

In 2005, Rwanda was experiencing a generalized HIV epidemic with 3% of the adult population living with HIV [9]. WHO estimated that the incidence of TB disease in Rwanda was 361 per 100,000 population and 41% of patients with TB disease were infected with HIV [10]. There were 161 TB clinics in Rwanda and all were using WHO's Directly Observed Treatment Short-Course (DOTS) strategy for the management of TB disease. New cases of pulmonary TB were treated with a standardized regimen of fixed-dose combinations of rifampicin, isoniazid, ethambutol, and pyrazinimide taken daily for two months (intensive phase) and then a fixed-dose combination tablet of rifampicin and isoniazid administered three days a week for four months (continuation phase). In 2005, patients with TB/HIV were eligible for antiretroviral therapy (ART) if they had a $CD4^+$ cell count < 350 cells/mm^3 [11]. For the majority of patients with TB/HIV, ART included efavirenz-based regimens initiated after completing the two month intensive phase of anti-TB treatment.

In response to the TB/HIV syndemic [12-14] and the new TB/HIV guidance from WHO, Rwanda's national TB program (NTP) drafted and approved a national policy on collaborative TB/HIV activities in December of 2005. The new national TB/HIV policy included provider-initiated HIV testing and counseling for all patients with TB as well as the provision of HIV care and treatment for patients with TB/HIV. Prior to implementing the policy and in the absence of nationally representative TB/HIV surveillance data, the NTP wanted to collect baseline data and identify possible barriers to routine HIV testing for patients with TB.

In October 2005, we evaluated current TB/HIV practices in health facilities providing TB services and identified possible barriers to implementing the new TB/HIV policy. The objectives of our evaluation were to 1) collect data to inform the national scale-up of HIV services in TB facilities, and to 2) provide baseline data by which to evaluate the scale-up of activities using national surveillance data. To inform the scale-up of activities we focused on assessing staff awareness of the relationship between TB and HIV, activities in support of TB/HIV coordination, determining what proportion of patients with TB were being offered HIV testing, evaluating the acceptability of HIV testing among patients with TB, and documenting whether or not patients with TB/HIV were receiving cotrimoxazole prophylaxis (CTX) and ART.

Methods

Baseline Evaluation

We conducted the evaluation in a non-probability sample of 23 of 161 (14%) TB clinics in Rwanda. The sample of TB clinics was selected by the NTP to represent all provinces of the country and include a mix of urban and rural health centers and hospitals providing TB diagnostic and treatment services.

The three evaluation components were 1) structured interviews with patients arriving at the clinics to receive their anti-TB medications, 2) structured interviews with staff working at the TB clinics, and 3) review of the TB registers and patient treatment cards for patients registered for anti-TB treatment during a specified three month period. All data collection forms were piloted and revised based on focus group discussions with patients receiving anti-TB treatment and staff working at the TB clinics of two sites not selected to participate in the evaluation. Data collectors fluent in Kinyarwanda, French, and English were trained to lead the focus group discussions. Data collection forms, focus group guides, and resultant transcripts were translated from English to Kinyarwanda and then back translated to ensure proper translation.

From October 1 to October 14, 2005, we collected baseline data using two teams consisting of staff from the NTP, CDC, and medical students from the National University of Rwanda. All data collectors participated in a two-day skills-based training on leading focus groups, conducting structured interviews, using the data collection tools, data entry, and ensuring the protection of study participants.

Structured interviews with patients

We approached the first 10 patients arriving for anti-TB treatment at each clinic. After receiving oral informed consent, we conducted structured interviews including both open and closed-ended questions. We interviewed patients to assess their experiences with HIV testing with a focus on what encouraged them or prevented them from getting HIV testing. For patients who disclosed being infected with HIV, we asked whether or not they were receiving CTX and ART. For patients not tested, we asked if they would accept HIV testing if offered and, if not, why?

Structured interviews with staff

We interviewed 1-2 staff at each clinic, depending on the number of staff working at the clinic and their work burden at the time of our visit. We asked staff open and closed-ended questions to assess their awareness of the association between TB and HIV, their knowledge of risk factors associated with TB disease, and the percentage of patients with TB offered HIV testing and counseling. We also asked them to describe any perceived barriers to offering HIV testing to patients with TB. Lastly, we asked about services routinely provided for patients with TB/HIV.

Review of TB registers and patient treatment cards

We reviewed the TB registers and patient treatment cards for all patients registered for anti-TB treatment

during the fourth quarter of 2004. We selected the fourth quarter of 2004, because we wanted to evaluate how HIV impacted the risk of death among people with TB and at the time of our evaluation these patients were the most recent quarterly cohort with documented treatment outcomes. Registers were reviewed to determine the proportion of patients with documented HIV test results prior to transitioning from VCT to PITC and to compare TB treatment outcomes for patients based on their HIV status. We abstracted data on patient demographics, TB diagnosis (pulmonary versus extrapulmonary), treatment category (new versus re-treatment), treatment outcome (cured, completed, died, defaulted, or transferred out), HIV status, and receipt of CTX and/or initiation of ART for patients with TB/HIV.

Evaluating the Scale-up of Collaborative TB/HIV Activities

We measured the scale-up of collaborative TB/HIV activities by comparing our baseline evaluation data to select TB/HIV indicators routinely collected by all TB clinics in Rwanda and reported to the national TB program. District level reports are compiled and transmitted to the NTP following quarterly district-level evaluation meetings. All districts report to the NTP and the quality and completeness of the TB/HIV data are routinely evaluated during supportive supervision visits. Using the nationally representative data provided by the Ministry of Health, we compared the proportion of patients with TB getting an HIV test, testing positive, and among those testing positive the proportion getting CTX and ART from 2005 to 2009. Our crude analysis of the risk of death among patients with TB/HIV relative to patients with TB not infected with HIV was limited to the years for which patients' anti-TB treatment outcomes could be linked to their HIV testing data (i.e., our baseline data and enhanced surveillance done in 2007).

Statistical analysis

We calculated descriptive statistics for data from each of the three components of the evaluation. We performed Pearson's X^2 test to examine the association between dying during anti-TB treatment and patients' HIV status. For our crude analysis of the risk of death during anti-TB treatment, we excluded patients who defaulted or transferred out because we could not determine whether they survived or died.

Ethical approval

The evaluation protocol underwent ethical review and was determined to be a program evaluation and not research by CDC, the Rwandan Ministry of Health, and Columbia University.

Results

Baseline Evaluation

All geographic regions of the country were represented by the sample of 23 TB clinics and the geographic distribution of the sample approximated the distribution of clinics nationally (Table 1). Our sample underrepresented health centers (48% of our sample relative to 70% nationally) and overrepresented district hospitals (44% of our sample relative to 20% nationally). On-site HIV testing and ART services were available at 74% and 65% of the health facilities in our sample compared to 70% and 41% of facilities nationally.

Structured interviews with patients

Of the 207 patients with TB we interviewed, 81 (39%) were female, median age was 37 years, 113 (55%) had completed primary school and 63 (30%) had no formal education. We interviewed an average of nine patients per site depending on the number of patients presenting at the clinics for treatment at the time of our site visits (range 1 to 14 patients interviewed per site). Patient consent to participate was nearly 100% with refusals being so rare that data collectors stopped routinely documenting them.

Of the 207 patients interviewed, 158 (76%) reported being offered an HIV test at the time of TB diagnosis. Of those, 157 (99%) accepted testing and received their results (Figure 1). Among 134 (85%) patients who disclosed their test results to interviewers, 66 (49%) reported a positive HIV test result. Among the 49 patients not offered a test, 9 had been previously tested and 32 of the 40 not previously tested (80%) responded

Table 1 Characteristics of evaluation sites and all TB facilities in Rwanda, 2005

	Evaluation Sites (n = 23)		All TB Facilities (N = 161)	
	No.	%	No.	%
Province				
Kigali City	4	18	22	14
Northern	5	22	22	14
Southern	6	26	42	26
Eastern	4	17	35	22
Western	4	17	40	24
Facility type				
Health center	11	48	113	70
District hospital	10	44	33	20
Referral hospital	2	8	4	3
Other	0	0	11	7
On-site HIV services				
VCT*	17	74	113	70
ART†	15	65	66	41

* VCT = Voluntary HIV Counseling and Testing

†ARV = antiretroviral therapy

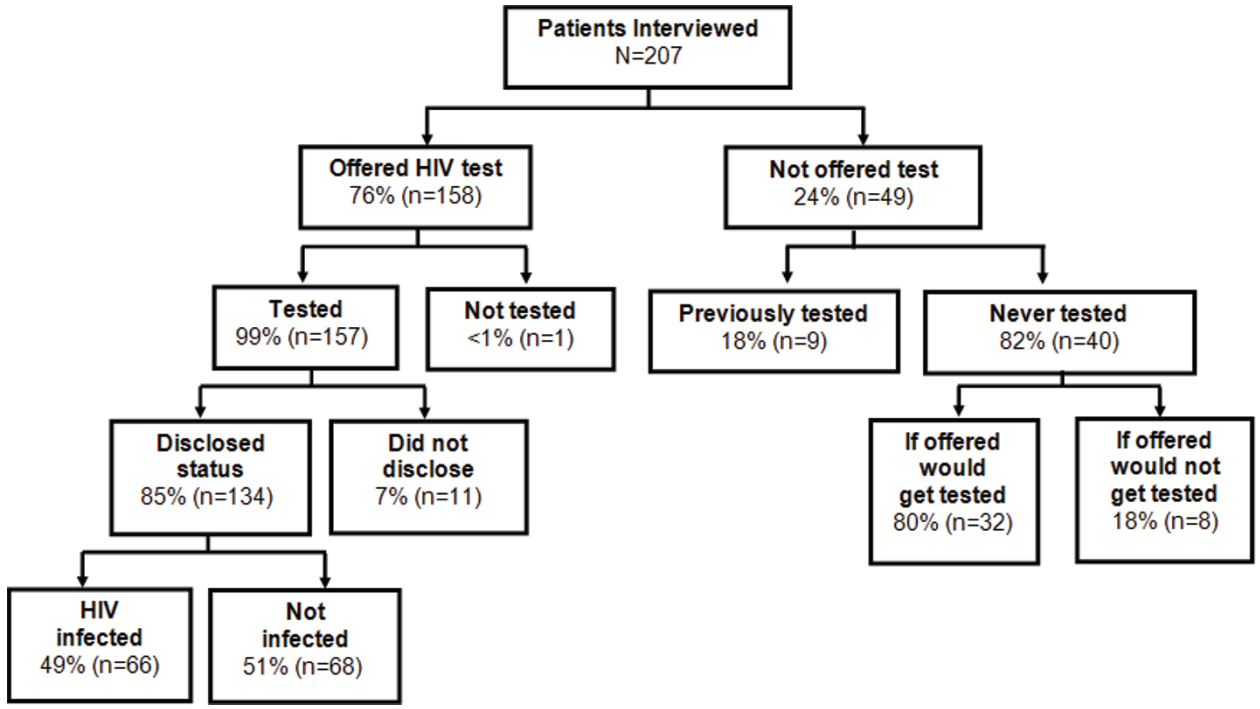

Figure 1 HIV Testing Among Patients with TB.

that they would accept HIV testing if it were offered to them by staff at the TB clinic. Overall, 81% (167/207) of patients knew their status either because they were offered and accepted testing or they had been previously tested.

Patients who reported accepting HIV testing in TB services (n = 157) were asked what convinced them to get tested. Patients could provide multiple responses with the most common reasons cited for getting an HIV test being the patient's desire to know their HIV status (71%, n = 110), recommendation by a health care worker (35%, n = 55), and possible exposure to HIV through unprotected sexual intercourse (25%, n = 38). Among the seven patients not offered a test, not previously tested, and who would refuse a test if offered; the most common reasons cited for not getting tested were that they did not perceive themselves to be at risk for HIV infection (n = 4) or feared a positive test result (n = 2).

Patients with TB/HIV were asked whether someone talked with them about starting CTX and/or ART and whether they had initiated ART. For the 66 patients who disclosed a positive HIV test result, 97% (64/66) recalled talking with someone about taking CTX to prevent opportunistic infections, 89% (59/66) reported meeting with someone to discuss ART, and 53% (35/66) responded that they were currently receiving ART.

Structured interviews with staff

We interviewed 40 staff from the 23 TB clinics, including 35 (88%) nurses, one nurse assistant, one medical assistant, one TB/HIV focal person, and one health center director. Staff awareness of the relationship between TB and HIV was evaluated by asking open-ended questions about risk factors for developing TB disease and the leading cause of death among PLHIV. Among the 40 staff, 35% (14/40) correctly identified TB disease as the leading cause of death among PLHIV. When asked to identify the most common risk factors for PLHIV developing TB disease, staff mentioned HIV infection or immune suppression (83%), contact with another person with TB disease (75%), malnutrition (58%), and poverty (13%).

When asked about the percentage of patients with TB offered HIV testing at their TB clinics, 11 (32%) staff reported their clinic offered testing to all patients, 16 (47%) reported their clinic offered to more than half of patients, seven (21%) to less than half of patients, and six did not know. We then asked staff to talk about barriers to offering HIV testing to patients with TB. The most frequently mentioned barriers as perceived by staff were lack of trained staff (43%), insufficient space for testing and counseling (33%), and patient concerns about stigmatization associated with HIV testing (25%) (Table 2).

Table 2 Barriers to offering HIV testing reported by TB clinic staff

	n*	(%)
Not enough trained staff	17	(43)
Not enough space	13	(33)
Patient's concern about stigma of test	10	(25)
Responsibility of VCT clinic	6	(15)
Not enough supplies	5	(13)
Staff uncomfortable offering the test	4	(10)

* Staff could give multiple responses

Lastly, we asked staff about services routinely provided for patients with TB after HIV testing and counseling. For patients with a positive HIV test result, 90% (36/40) of staff reported that patients at their facility receive counseling, 65% (26/40) receive ART, 65% (26/40) CTX, 65% condoms, and 10% (4/40) nutritional support. For patients with a negative HIV test result, 93% (37/40) of staff reported providing counseling on risk reduction, 58% (23/40) assessed patient's risk of HIV infection, 35% (14/40) offered condoms only to patients believed to be at high risk for HIV infection and 10% (4/40) offered condoms to all patients.

Review of TB registers and patient treatment cards

During the fourth quarter of 2004 (the most recent cohort with treatment outcomes at the time of our baseline evaluation) there were 542 patients registered for anti-TB treatment at the 23 TB clinics; 211 (39%) were female and the mean age of patients was 32.8 years (SD 14.1) (Table 3). Overall, 77% (n = 416) of patients were diagnosed with pulmonary disease and 80% (435/542) were new patients with no known history of being previously treated for TB disease. HIV test results were documented in the TB register for 48% of patients (n = 258), in the patient treatment cards for 38% (n = 208), and either the TB register or patient treatment cards for 52% (n = 282) of patients. Among patients with a documented HIV test, 44% (122/277) had a positive test result. Of the 122 patients with a positive HIV test result, there was documentation in the register or their patient treatment cards that 2.5% (3/122) were receiving CTX and 12.3% (15/122) had initiated ART.

Among patients with documented anti-TB treatment outcomes, 69% (n = 336) had successful outcomes (i.e., either cured or completed) and 11.1% (n = 60) died before completing anti-TB treatment. Treatment outcomes differed based on patients' HIV status (Table 4). The crude risk of death among patients with TB/HIV was 6.1 (95% CI 2.6, 14.0) times the risk among patients with TB not infected with HIV. The crude risk of death among patients with TB and undocumented HIV status was 2.9 (95% CI 1.2, 6.9) times the risk among patients with TB not infected with HIV.

Table 3 Patient and disease characteristics and TB treatment outcomes (N = 542 patients registered during the 4th Quarter of 2004)

Characteristic	No.	(%)
Female	211	(38.9)
Mean age in years	32.8	SD*14.2
Pulmonary TB	416	(76.8)
New patient	435	(80.3)
HIV Status		
Positive	122	(22.5)
Negative	155	(28.6)
Not documented	265	(48.9)
Treatment outcomes†		
Cured	198	(36.5)
Completed	138	(25.5)
Died	60	(11.1)
Defaulted	15	(2.8)
Transferred out	76	(14.0)

*SD = standard deviation

† Missing outcomes for 10.1% (n = 55) of patients registered

Evaluation of the Scale-up of Collaborative TB/HIV Activities

The proportion of patients with TB having HIV test results documented in the TB register increased from 48% during our baseline evaluation to 69% during the first year of scale-up in 2005, and then increased to 97% in 2009 (Figure 2). Provision of CTX for people with TB/HIV increased from the 2.5% noted during our evaluation to 15% in 2005 and then to 92% in 2009 [12,13]. The proportion of people with TB/HIV initiating ART increased from the 12.5% at baseline to 13% in 2005 and 49% in 2009 [15,16]. The most recent year with reported data on anti-TB treatment outcomes stratified by HIV status was 2007 and the risk of death during anti-TB treatment among patients with TB/HIV was 1.8 times greater (95% CI 1.68, 1.94) than the risk among patients with TB not infected with HIV [16]. The relative risk of death in 2007 (RR = 1.8, 95% CI 1.68, 1.94) was less than the relative risk calculated for patients in

Table 4 TB treatment outcomes* by HIV status for patients registered during the 4th quarter of 2004 (n = 358)

	Treatment success		Died		Risk of death	
	n	(%)	N	(%)	RR	95% CI
HIV positive (n = 90)	63	(70)	27	(30)	6.1	(2.6 -14.0)
HIV negative (n = 121)	115	(95)	6	(5)	Referent	Referent
HIV unknown (n = 147)	126	(86)	21	(14)	2.9	(1.2-6.9)

* Analysis limited to patients with anti-TB treatment outcomes of success (cured and completed) or death

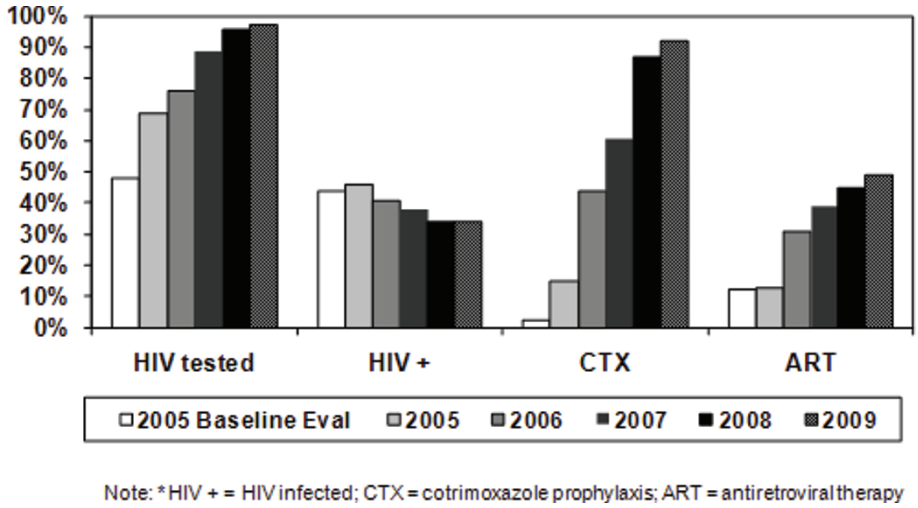

Figure 2 Trends in HIV testing, HIV infection, and HIV care and treatment for patients with TB in Rwanda, baseline evaluation data from 2005 and nationally reported data from 2005 - 2009.

our 2005 baseline evaluation with confidence intervals that did not overlap (RR = 6.1, 95% CI 2.6, 14.0).

Discussion

We conducted this evaluation to collect baseline data to support and inform the implementation and ongoing scale-up of the new national TB/HIV policy in Rwanda. Multiple data sources were used in order to compare and contrast what patients reported, what staff reported, and what was documented about HIV testing for patients with TB and care and treatment for patients with TB/HIV. Our interpretations of the evaluation data were that patients with TB and staff at TB clinics were receptive to HIV testing which supports the premise that TB clinics could be an important point of entry into life-saving HIV care and treatment services in Rwanda. Review of subsequent programmatic data confirms the success of the national scale-up of key TB/HIV services and suggests a substantial public health impact from these efforts.

From patient interviews we learned that when offered, almost all patients (99%) reported accepting HIV testing. The almost universal acceptance of HIV testing by patients and the stated willingness to accept testing by patients not offered HIV testing, suggested that implementing routine PITC for all patients with TB disease could dramatically increase testing uptake. However, interviews with TB clinic staff revealed that less than a third of staff reported offering HIV testing to all patients with TB and only 38% knew that TB was the leading cause of death among PLHIV. Additionally, our review of patient records revealed that there was no documentation of HIV test results for almost half (48%) of patients registered for TB treatment. The lack of documentation indicated that staff were either not routinely offering or documenting HIV testing. Inconsistent documentation of HIV information could result in missed opportunities for eligible patients to initiate ART and underestimation of the burden of disease and resources needed to treat TB/HIV. Similarly, based on available data it was not possible to determine how much of the change in the proportion of patients receiving CTX or ART is due to enhanced services versus improved data recording and reporting. These discrepancies identified during our evaluation highlight the importance of routinely evaluating surveillance systems to ensure completeness and accuracy of surveillance data. To support the scale-up of TB/HIV activities, resources were needed to train staff about the relationship between TB/HIV and the importance of routinely offering HIV testing and documenting patients' test results.

The proportion of patients with TB disease and HIV infection based on patient interviews (49%) and clinical record reviews (42%) were consistent with the national data (46%) in 2005. Patients with TB and HIV infection were more likely to die during anti-TB treatment than patients with TB not infected with HIV. Also, our finding that patients with unknown HIV status had a greater risk of death than patients with HIV negative test results suggests that the group with unknown HIV serostatus probably contained people with undiagnosed HIV. Our finding of an increased risk of death during anti-TB treatment for people infected with HIV is consistent with other published reports [17,18] and highlights the importance of routine HIV testing to minimize delays in HIV diagnosis and initiation of ART to reduce the risk of death among patients with TB/HIV [19-21].

Expanded access to HIV testing, care, and treatment were urgently needed based on the proportion of patients with unknown HIV status, the high rate of HIV infection coupled with poorer TB treatment outcomes, and the lack of documented CTX and ART for patients with TB/HIV.

In response to the evaluation findings, the MOH modified their draft TB/HIV policy in November 2005, to specify that CTX should be routinely provided through the TB program for all patients with TB/HIV. Evaluation findings were used to plan and implement national, regional, and district trainings on PITC and to ensure that patients with TB/HIV receive CTX and ART when indicated. The National TB and HIV Programs led the implementation of TB/HIV collaborative activities, starting with revision of program guidelines, training materials, and monitoring and evaluation tools. TB/HIV collaborative activities were implemented and refined at two model centers prior to national scale-up. An assessment was conducted to identify the training needs of health service staff to inform the development and decentralized implementation of an integrated TB/HIV curriculum. The curriculum emphasized cross-training and was implemented with staff at district-level health facilities providing quality assured TB diagnostic and treatment services and ART. The two model centers were used as practical training centers and implementation fidelity was assured through intensive site support visits that included clinical mentorship and ongoing monitoring and evaluation of key indicators.

Rwanda has achieved dramatic increases in HIV testing and provision of CTX and ART for patients with TB/HIV [22-24]. The risk of death among patients with TB/HIV has decreased as HIV testing and the provision of CTX and ART has been scaled-up. The noted decrease in the relative risk of death among patients with TB/HIV (from 6.1 to 1.8 with non-overlapping confidence intervals) is encouraging but should be interpreted with caution because the comparison is based on cross-sectional data.

In 2006, in response to increasing evidence that early initiation of ART substantially improves the survival of patients with TB/HIV [25], Rwanda began implementing a "one-stop" TB-HIV integrated services model where ART is provided to patients with TB/HIV at TB Diagnostic and Treatment Centers (DTC). By April 2009, the "one-stop" TB-HIV integration model had already been adopted by 80% (153 of 192) of TB clinics (personal communication with Director of the NTP), which should further expand ART coverage for people with TB/HIV. The NTP aims to reach 100% coverage of CTX as it is a relatively inexpensive, safe, and life-saving intervention [26]. Evaluation research is now needed to document the operationalization and impact of the "one-stop" approach, especially in light of the WHO's "3 I's" initiative (intensified TB case-finding, isoniazid preventive therapy, and infection control), which calls for greater integration and provision of services for people with TB/HIV [27].

Our evaluation findings were based on a non-probability sample of TB clinics, staff, and patients, and therefore may not have been representative of all TB clinics in the country. Despite the higher proportions of district and referral hospital-based clinics in our non-probability sample compared with national TB clinics, we do not believe that the former was biased towards selecting "top-performing sites," as the performance indicators (e.g., HIV testing, provision of CTX/ART) from our sample were lower than national estimates from 2005. Data from patients and health care workers were based on self-report and therefore are subject to recall and social desirability bias. Data from healthcare workers or TB registers on the provision of ART underestimate the uptake of ART because the denominator includes an undeterminable number of patients with TB who were not eligible for ART based on their CD4 cell counts (note: the CD4 threshold below which people are eligible for ARVs increased from 200 to 350 in 2008). We were unable to ascertain the true outcome status of patients receiving anti-TB treatment who had defaulted, which may have resulted in an underestimation of mortality. Despite the aforementioned limitations, our baseline estimates of HIV infection among patients with TB and provision of CTX and ART for patients with TB/HIV were consistent with 2005 national estimates that were released after our evaluation. We were not able to perform survival analyses and our estimates of the risk of death during TB treatment are unadjusted because patient-level data for possible confounders were not available.

Conclusions

Using three sources of data, we were able to demonstrate that patients and staff were receptive to HIV testing and that TB clinics could serve as a point of entry into HIV care and treatment. Patients' acceptance of and staff willingness to offer HIV testing refuted concerns that stigma or increased work load were barriers to routine PITC and provided further evidence for routinely offering testing. Introduction of PITC during rapid scale-up of HIV care and treatment services in Rwanda resulted in people being diagnosed and treated for HIV who otherwise would likely have had delayed diagnoses or died of undiagnosed HIV disease [28,29]. Rwanda provides a model for integrating TB-HIV services that has resulted in the majority of patients with TB knowing their HIV status and a dramatic scale-up of lifesaving HIV care and treatment that coincided with a decline in the risk of death among patients with TB/HIV.

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Authors' contributions
EP has full access to all the study data and accepts responsibility for the integrity and accuracy of the data and data analysis. EP, GV, MG, and AF conceptualized and designed the study. Acquisition of data was done by EP, GV, and AF Statistical analyses were done by EP, DL, AF, and interpretation of the data was done by EP, GV, DL, MG, and AF Drafting of the manuscript was done by EP and DL with critical revisions for intellectual content provided by GV and AF. All authors have read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

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Influenza Sentinel Surveillance in Rwanda, 2008–2010

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Background. In 2008, Rwanda established an influenza sentinel surveillance (ISS) system to describe the epidemiology of influenza and monitor for the emergence of novel influenza A viruses. We report surveillance results from August 2008 to July 2010.

Methods. We conducted ISS by monitoring patients with influenza-like illness (ILI) and severe acute respiratory infection (SARI) at 6 hospitals. For each case, demographic and clinical data, 1 nasopharyngeal specimen, and 1 oropharyngeal specimen were collected. Specimens were tested by real-time reverse-transcription polymerase chain reaction for influenza A and B viruses at the National Reference Laboratory in Rwanda.

Results. A total of 1916 cases (945 ILI and 971 SARI) were identified. Of these, 29.2% (n = 276) of ILI and 10.4% (n = 101) of SARI cases tested positive for influenza. Of the total influenza-positive cases (n = 377), 71.8% (n = 271) were A(H1N1) pdm09, 5.6% (n = 21) influenza A(H1), 7.7% (n = 29) influenza A(H3), 1.6% (n = 6) influenza A (unsubtyped), and 13.3% (n = 50) influenza B. The percentage of positivity for influenza viruses was highest in October–November and February–March, during peaks in rainfall.

Conclusions. The implementation of ISS enabled characterization of the epidemiology and seasonality of influenza in Rwanda for the first time. Future efforts should determine the population-based influenza burden to inform interventions such as targeted vaccination.

Influenza virus infection is a major public health concern worldwide, resulting in an estimated 500 000 deaths annually [1–9]. The epidemiology of influenza is well characterized in the temperate areas of the Northern and Southern Hemispheres [2]. However, little is known about the epidemiology, seasonality, and burden of influenza in tropical areas, especially in sub-Saharan Africa, where the severity of infections is likely compounded by malnutrition, limited supplies of antibiotics to treat secondary bacterial infections [1], poverty, and poor access to healthcare [3].

Rwanda is a landlocked developing country with an area of 26 338 km^2, situated in Central Africa immediately south of the equator. It has an equatorial climate with moderate temperatures and 2 rainy seasons, from March through June and from October through December. The average annual temperature ranges from 18°C to 24°C. Given the small geographical extent of the country, no climatic differences are observed [10]. The 2010 estimated population is approximately 10.4 million and the population density (350 persons/km^2) is among the highest in sub-Saharan Africa [11].

Prior to 2008, there was no surveillance for influenza in Rwanda. In July 2008 the Rwandan Ministry of Health, in collaboration with the US Centers for Disease Control and Prevention (CDC), established an influenza sentinel surveillance (ISS) system with the following objectives: to describe the epidemiology and seasonality of influenza, to monitor for the emergence of novel influenza viruses, to describe the circulating influenza virus types and subtypes, and to detect influenza outbreaks in a timely manner.

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METHODS

Sentinel Sites

From July 2008 to May 2009, sentinel surveillance was established in 4 public hospitals. In May 2009, following the emergence of influenza A(H1N1)pdm09 in North America in April 2009, the surveillance was extended to 2 additional sites (Supplementary Figure 1). Sentinel sites represented the country's 5 regions, and selection required capacity to collect and ship samples to the National Reference Laboratory (NRL) in Kigali and the site's interest in participating in the ISS program. Each hospital had pediatric, adult, and maternity inpatient wards and ambulatory care services, and all services participated in the ISS. One referral hospital and one district hospital were located in the capital city of Kigali, while the other 3 district hospitals and 1 referral hospital were located in each of the country's 4 provinces. Each district hospital's catchment population was estimated to be approximately 300 000 persons [11]. Unlike district hospitals, the true catchment populations of referral hospitals are unknown since people from all over the country attend referral hospitals for primary and secondary care.

Surveillance Protocol

The Pan American Health Organization/CDC Generic Protocol for Influenza Sentinel Surveillance [12] was adapted to generate a country-specific protocol for the ISS. At each sentinel site, 2 syndromic case definitions were used—influenza-like illness (ILI) and severe acute respiratory infection (SARI). An ILI case was defined as an outpatient aged ≥2 months with fever ≥38°C and cough or sore throat in the absence of another diagnosis, with symptom onset within 72 hours of presentation. A SARI case in persons ≥5 years of age was defined as a hospitalized patient with fever ≥38°C, cough, and shortness of breath or difficulty breathing, with the onset of signs and symptoms within 7 days of presentation. The SARI case definition for children 2 months through <5 years of age was based on the World Health Organization's Integrated Management of Childhood Illness (IMCI) definition for pneumonia and severe pneumonia [13], and was defined as a hospitalized patient with cough or difficulty breathing, and at least 1 danger sign (unable to drink or breastfeed, lethargic or unconscious [ensure patient is awake], vomits everything [not only occasional], convulsions, nasal flaring, grunting, oxygen saturation <90%, chest indrawing [retractions under ribcage on inspiration], stridor in a calm child, tachypnea [2 months–1 year: relative risk (RR) >50; 1 year–5 years: RR > 40]), with symptom onset within 7 days of presentation. Infants aged <2 months with fast breathing (≥60 breaths per minute) were excluded as they are referred for severe bacterial infection. Cases were identified by dedicated surveillance officers (eg, trained nurses) in collaboration with clinicians providing treatment. For all eligible SARI cases and the first 2 ILI cases each day, a questionnaire was completed that included demographic, clinical, and epidemiological information. In addition, a nasopharyngeal and an oropharyngeal swab were collected from each patient and placed in the same cryovial containing 1 mL of viral transport medium and stored at 4°C on site for a maximum of 72 hours until they could be shipped to the NRL.

At the NRL, RNA extractions were performed on specimens stored at −70°C using the QIAamp Viral RNA Isolation Kit (Qiagen). Extracted RNA was amplified using commercially prepared master mix (Invitrogen Corp) and primers provided by the CDC using standard real-time reverse-transcription polymerase chain reaction (RT-PCR) procedures using 7500 standard real-time PCR system (Applied Biosystems) to detect for the presence of human ribonucleoprotein (RNP) and influenza type A and B viruses. Influenza A–positive specimens were further subtyped with H1, H3, H5, and A(H1N1)pdm09 subtypes. The RNP was assessed to see whether or not the samples contain sufficient human cells for internal quality control purposes [14, 15].

Meteorological Data

We obtained data from the Rwandan meteorological service for temperature, relative humidity, and rainfall during the surveillance period from August 2008 through July 2010.

Data Analysis

We assessed the demographic, clinical, and epidemiological characteristics of influenza positive and negative ILI and SARI cases as well as the temporal patterns of influenza virus circulation. Bivariate analysis was performed using χ^2 and Fisher exact tests with P values ≤.05. Multivariate logistic models were used to assess the association of influenza positivity with age group, sex, rainfall, temperature, humidity, and 7 other risk factors (Table 1). Model selection was performed using a backward selection (probability of entry [pe] = 0.05 and pe = 0.10). The final model is an additive model that retains a total of 7 covariates. For this analysis, interaction among different covariates was not assessed. EpiInfo version 3.5.1 (CDC) and Stata software version 10 (StataCorp) were used for the analysis.

Ethics Statement

The ISS protocol was reviewed and deemed to be nonresearch by the Rwandan Ministry of Health and the CDC. Verbal consent was obtained from all patients prior to data and specimen collection. For children aged <15 years, verbal consent was obtained from a parent or legal guardian.

RESULTS

Demographic and Exposures Among ILI and SARI Cases

From August 2008 through July 2010, we enrolled 1916 cases (ILI, n = 945; SARI, n = 971). Among SARI cases, 71.8% (697/

Table 1. Demographic and Epidemiological Characteristics of Influenza-like Illness and Severe Acute Respiratory Infection Cases, Rwanda (August 2008–July 2010)

	ILI (n = 945)			SARI (n = 971)[b]		
Parameters	Influenza Negative	Influenza Positive	*P* Value	Influenza Negative	Influenza Positive	*P* Value
Number (%)	669 (70.8)	276 (29.2)		870 (89.6)	101 (10.4)	
Age						
Median, y(95% CI)	21 (19.6–23)	19 (16–20)	.02	1 (1–1)	4 (2–6)	.001
Range	2 mo–86 y	3 mo–62 y		2 mo–93 y	2 mo–77 y	
<6 mo	32 (4.78)	1 (0.4)	<.001	85 (9.8)	3 (3.0)	<.001
6–23 mo	113 (16.9)	26 (9.4)		380 (43.7)	32 (31.7)	
24–59 mo	75 (11.2)	17 (6.2)		178 (20.5)	19 (18.8)	
5–14 y	48 (7.2)	70 (25.4)		77 (8.9)	18 (17.8)	
15–49 y	375 (56.1)	156 (56.5)		107 (12.3)	25 (24.8)	
50–64 y	20 (3.0)	6 (2.2)		30 (3.5)	3 (3.0)	
≥65 y	6 (0.9)	0 (0.0)		13 (1.5)	1 (1.0)	
Sex						
Female	375 (56.1)	142 (51.4)	.196	434 (49.9)	47 (46.5)	.524
Risk factors						
Pregnant[b]	9 (1.4)	2 (0.7)	.332	8 (0.9)	1 (1.0)	.621
Office worker	25 (3.7)	14 (5.1)	0.221	1 (0.1)	1 (1.0)	.197
Student	82 (12.3)	98 (35.5)	<.001	38 (4.4)	16 (15.8)	<.001
Healthcare worker	76 (11.4)	28 (10.2)	.648	9 (1.0)	5 (5.1)	.009
Children at home	177 (26.6)	149 (54.0)	<.001	172 (19.9)	26 (26.5)	.146
Close contact with similar illness in last 3 wk	51 (7.8)	39 (14.4)	0.003	75 (8.8)	13 (13.3)	.144
Close contact with a person who died of undiagnosed acute respiratory illness	5 (0.8)	3 (1.1)	.703	3 (0.4)	0 (0.0)	.723

Data are presented as no. (%) unless otherwise specified.

Abbreviations: CI, confidence interval; ILI, influenza-like illness; SARI, severe acute respiratory infection.

[a] Among cases in women of childbearing age (15–49 y).

[b] SARI definition differed for <5 y.

971) were <5 years of age whereas among ILI, 72% (681/945) were >5 years of age. The ratio of males to females was 0.83 for ILI and 1.02 for SARI cases. The median age was 19 years (range, 2 months–86 years) for ILI and 3 years (range, 2 months–93 years) for SARI cases. Among ILI and SARI cases, 29.2% (276/945) and10.4% (101/971), respectively, tested positive for influenza. Influenza was associated with age and the influenza detection rate was higher in those aged 5–14 years ($P < .01$; odds ratio [OR], 8.145) and 15–49 years ($P < .01$; OR, 4.89) for both ILI and SARI cases followed by those aged 6–23 months ($P < .05$; OR, 3.266) for SARI cases (Tables 1 and Supplementary Table 2). In all categories, few cases reported pregnancy (1.0%), office worker (2.1%), or healthcare worker status (6.2%). Risk factor analysis showed that student status (12.2%) (OR, 1.667; 95% confidence interval [CI], .164–2.287) and having children at home (27.3%) (OR, 1.842; 95% CI, .406–2.414) were significantly more frequent exposures in influenza-positive ILI cases compared to influenza-negative ILI cases.

Clinical Presentation

For all case types, and for influenza-positive and influenza-negative cases, fever, cough, headache, sore throat, and lethargy were the most common symptoms reported at illness onset (Supplementary Table 1). Nausea and headache were significantly more frequent in influenza-positive compared with influenza-negative cases ($P < .05$).

Among all SARI- and ILI-positive influenza cases, the median temperature on presentation was similar, ranging from 38.2°C to 38.7°C (Supplementary Table 1). The median pulse oximetry on presentation was 97% (range, 90–100) for influenza-positive ILI cases, 95% (range, 72–100) for influenza-positive SARI cases (Supplementary Table 1). There was no difference in pulse oximetry on presentation between influenza-positive and influenza-negative cases. The median time from symptom onset to presentation was also similar among influenza-positive and influenza-negative cases and was 3 days (range, 1–14 days) for influenza-positive ILI cases, 3.5 days (range, 2–15 days) for influenza-positive SARI cases. Of all

Table 2. Influenza Type and Subtypes Among Influenza-like Illness and Severe Acute Respiratory Infection Cases by Age Group in Rwanda (August 2008–July 2010)

	Age Group							
Influenza Type	<6 mo n = 121	6–23 mo n = 551	24–59 mo n = 289	5–14 y n = 213	15–49 y n = 663	50–64 y n = 59	≥65 y n = 20	Total N = 1916
B	2 (1.7)	15 (2.7)	2 (0.7)	5 (2.3)	24 (3.6)	1 (1.7)	1 (5.0)	50 (2.6)
A(H1) Seasonal	1 (0.8)	1 (0.2)	0 (0.0)	5 (2.3)	13 (2.0)	1 (1.7)	0 (0.0)	21 (1.1)
A(H3) Seasonal	1 (0.8)	6 (1.1)	3 (1.0)	5 (2.3)	10 (1.5)	4 (6.8)	0 (0.0)	29 (1.5)
A (unsubtyped)	0 (0.0)	1 (0.2)	1 (0.3)	1 (0.5)	3 (0.5)	0 (0.0)	0 (0.0)	6 (0.3)
A(H1N1)pdm09	3 (2.5)	31 (5.6)	28 (9.7)	74 (34.7)	132 (19.9)	3 (5.1)	0 (0.0)	271 (14.1)
Total	7 (5.8)	54 (9.7)	34 (11.7)	90 (42.3)	182 (27.5)	9 (15.3)	1 (5.0)	377 (19.6)

All data are presented as no. (%).

Abbreviations: ILI, influenza-like illness; SARI, severe acute respiratory infection.

positive influenza ILI cases, 68.1% and 98.9% presented within 3 days and 7 days of symptom onset, respectively. For all positive influenza SARI cases, 50% and 95% presented within 3 days and 7 days, respectively, of symptom onset. The mean duration of hospitalization was 5 days for 58 influenza-positive SARI cases with medical records available. The duration of hospitalization ranged from 2 to 15 days except for 1 patient who had influenza A(H3) coinfection with hepatitis C and tuberculosis for whom the hospital stay was 42 days.

Influenza Types and Subtypes

Of all influenza cases detected during the surveillance period, 86.7% (n = 327) were influenza A viruses and 13.3% (n = 50) were influenza B viruses (Supplementary Table 2). The majority of influenza in the 2008 season (July–December) was caused by influenza A(H3) viruses. In the 2009 season (January–December), initially, influenza A(H3) viruses predominated, with some cocirculation of influenza A(H1) viruses, but in October, 2009 influenza A(H1N1)pdm09 largely replaced all other influenza viruses. In 2010 (January–July), influenza A(H1N1) pdm09 continued to predominate even though it cocirculated with influenza A(H3) and influenza B.

The peaks in the percent positivity for influenza were seen in October–November 2008, February–March 2009, October–November 2009, and February–March 2010, roughly coinciding with the peaks in rainfall (Figure 1). During these same periods, overall numbers of SARI and ILI cases were higher. Overall, the temperature during this period was very stable but became slightly cooler with the onset of the rainy seasons. Analysis showed that there was significant association of influenza positivity with average monthly rainfall ($P < .001$) and average monthly relative humidity ($P < .05$). An increasing trend was found between rainfall and percent positivity of influenza (OR, 1.197; 95% CI, .996–1.439) (Supplementary Figure 2).

DISCUSSION

This is the first description of the seasonality and epidemiology of influenza in Rwanda. Key findings from this 24-month surveillance period relate to seasonality and influenza A and B viruses type and subtypes for the ultimate purpose of vaccine development, monitoring trends in virus spread and virus variations compared to annually recommended vaccines strains.

Although influenza viruses were detected year-round, there appear to be 2 distinct periods of increased transmission of influenza viruses annually, in February–March and October–November, which match the peak rainy seasons. These findings are consistent with patterns observed in some other tropical countries, including Bangladesh, Kenya, Lao People's Democratic Republic (Lao PDR), Singapore, and Thailand, where increased influenza activity was associated with increased rainfall [5, 7, 16–20]; also, in some of these countries, increased influenza activity was associated with higher relative humidity and higher temperatures.

The virologic surveillance of influenza during these 2 years in Rwanda revealed that influenza A virus circulation predominated over influenza B virus circulation: in 2008, influenza A (H3) subtype viruses predominated; in 2009 and 2010, influenza A(H1N1)pdm09 viruses predominated. These findings are consistent with circulation patterns documented in South Africa by the viral watch program, where in 2009, influenza A (H3) was the dominant influenza virus subtype before influenza A(H1N1)pdm09 was detected [21]. In Kenya, similar patterns were observed with a predominance of influenza A(H3) subtype in 2008 [22].

Influenza virus infection was detected in all age groups, but the relative proportion of positive influenza cases among SARI cases <5 years of age was low compared to the high proportion of SARI cases <5 years of age. This could represent the fact that other respiratory pathogens, including respiratory syncytial virus, play a more important role in respiratory syndromes

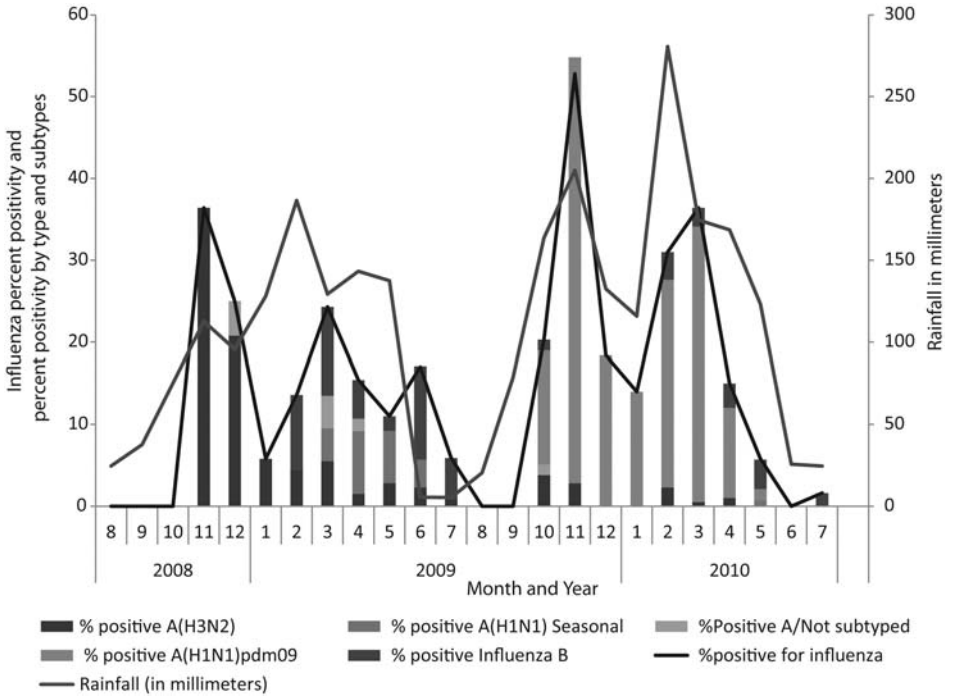

Figure 1. Percentage of positivity of influenza by influenza types and subtypes, rainfall by month, Rwanda (August 2008–July 2010).

in young children [1, 23]. Finally, in Rwanda, influenza was associated with 10.4% of SARI cases. The proportion of influenza positivity among hospitalized pneumonia cases is consistent with findings from Lao PDR, Peru, and Argentina and offers further evidence that a considerable proportion of pneumonia is associated with seasonal influenza [1, 4, 9, 16, 17, 19, 23]. The proportion of 29.2% influenza-positive (influenza A and B) among ILI cases is consistent with 34.8% found in Peru from samples collected during routine surveillance [24]; however, it is higher than results from national hospital-based surveillance in Bangladesh, where 10% of outpatient ILI case-patients had influenza [8]. The median length of hospital stay is consistent with 4 days (range, 0–42 days) across all age groups reported in Thailand [16]. The higher proportion of influenza among school-aged children suggests that school-based interventions (eg, school closures, vaccination) may be worth considering for preventing or mitigating influenza outbreaks in Rwanda.

There are several important limitations to the data gathered through this surveillance system. First, while we were able to obtain epidemiologic data, we were not able to estimate the burden of influenza because our surveillance system currently does not capture denominator data. Understanding the proportion of influenza-associated outpatient and inpatient visits and influenza virus infection rates in the population could inform policy decisions about interventions such as use of influenza vaccine. Second, our surveillance system does not perform viral culture and isolation of RT-PCR–positive influenza viruses, and subsequently does not perform any genetic and antigenic characterization of the circulating influenza. Therefore our data are limited to identifying influenza virus types and influenza A virus subtypes, and we do not have information on circulating strains and antiviral sensitivities. Finally, there are only 24 months of data available, including the period of initial implementation of the system, which limits the ability to establish clear temporal and seasonal influenza trends across the surveillance sites.

In conclusion, we found that influenza causes inpatient and outpatient disease year-round in Rwanda, with seasonal peaks during rainy periods. The molecular diagnostic methods allowed the NRL to promptly detect the influenza A(H1N1) pdm09 and to timely respond appropriately.

Future efforts should focus on continuing to strengthen the surveillance system, including evaluating the case definitions, ensuring that the system is capturing cases at high-risk of severe disease, adding viral culture, and introducing population-based methods to estimate disease burden.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Innovative strategies for a successful SLMTA country programme: The Rwanda story

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Background: In 2009, to improve the performance of laboratories and strengthen healthcare systems, the World Health Organization Regional Office for Africa (WHO AFRO) and partners launched two initiatives: a laboratory quality improvement programme called Strengthening Laboratory Management Toward Accreditation (SLMTA), and what is now called the Stepwise Laboratory Quality Improvement Process Towards Accreditation (SLIPTA).

Objectives: This study describes the achievements of Rwandan laboratories four years after the introduction of SLMTA in the country, using the SLIPTA scoring system to measure laboratory progress.

Methods: Three cohorts of five laboratories each were enrolled in the SLMTA programme in 2010, 2011 and 2013. The cohorts used SLMTA workshops, improvement projects, mentorship and quarterly performance-based financing incentives to accelerate laboratory quality improvement. Baseline, exit and follow-up audits were conducted over a two-year period from the time of enrolment. Audit scores were used to categorise laboratory quality on a scale of zero (< 55%) to five (95% – 100%) stars.

Results: At baseline, 14 of the 15 laboratories received zero stars with the remaining laboratory receiving a two-star rating. At exit, five laboratories received one star, six received two stars and four received three stars. At the follow-up audit conducted in the first two cohorts approximately one year after exit, one laboratory scored two stars, five laboratories earned three stars and four laboratories, including the National Reference Laboratory, achieved four stars.

Conclusion: Rwandan laboratories enrolled in SLMTA showed improvement in quality management systems. Sustaining the gains and further expansion of the SLMTA programme to meet country targets will require continued programme strengthening.

Introduction

Reliable laboratory services are vital to a high-quality healthcare system; thus, investing in laboratory quality improvement is not only valuable, but essential.[1] Despite a multitude of efforts to strengthen laboratories through infrastructure and human resource development, laboratory quality remains a challenge in resource-poor settings.[2,3]

Accreditation is a critical measure of a laboratory's quality level, as recognised by a series of international conventions, which called for accreditation to be part of laboratory-strengthening efforts in low-income countries.[4,5,6,7] In order to help address deficiencies in the system, two initiatives were launched concurrently in Kigali, Rwanda in July 2009 by the World Health Organization's Regional Office for Africa (WHO AFRO) and partners.[4] These were: Strengthening Laboratory Management Toward Accreditation (SLMTA), an innovative training and mentoring programme designed to facilitate the implementation of laboratory quality management systems in resource-limited settings;[8] and an incremental laboratory accreditation preparation process, which later became known as the Stepwise Laboratory Quality Improvement Process Towards Accreditation (SLIPTA).[9]

Rwanda has a tiered laboratory system, funded through the Ministry of Health, which consists of the National Reference Laboratory (NRL) overseeing the entire laboratory network, four central referral laboratories, 43 district hospital laboratories and approximately 500 health centre laboratories. The NRL and five of the district hospital laboratories receive additional funding as part of the East African Public Health Laboratory Network (EAPHLN), a World Bank project aimed at controlling epidemics by strengthening laboratory capacity in five East African countries.

To date, Rwanda has enrolled 15 laboratories (three cohorts of five each) in the SLMTA programme. The Ministry of Health aims to eventually enrol all national, central and district

hospital laboratories, a total of 48 countrywide, in the accreditation preparation process.[9] This study describes the achievements of the first three cohorts of the SLMTA programme and shares their experiences and lessons learned four years after the launch of the programme in Rwanda.

Research method and design

SLMTA sites and training

In January 2010, the Rwandan Ministry of Health enrolled its NRL, three central referral laboratories (Centre Hospitalier Universitaire de Kigali [CHUK], Centre Hospitalier Universitaire de Butare [CHUB] and King Faisal Hospital [KFH]), as well as one military hospital, Kanombe Military Hospital (KMH), into the first cohort of SLMTA (Cohort I). Twenty-three participants were trained: three from CHUK (one laboratory manager and two laboratory technologists), three from CHUB (one laboratory manager and two laboratory technologists), three from KMH (one medical doctor in charge of paediatrics and two laboratory technologists), three from KFH (one laboratory manager and two heads of units) and 11 from the NRL (two laboratory managers and nine heads of different sections). During the nine-month programme, participants attended three SLMTA workshops and implemented assigned improvement projects.

The second SLMTA cohort (Cohort II) began in November 2011 with the five district hospital laboratories funded by the EAPHLN project: Byumba, Gihundwe, Gisenyi, Kibungo and Nyagatare. The training included 14 participants from these laboratories, three participants each from four laboratories (one lab manager, one quality officer and one safety officer) and two from Nyagatare Hospital Laboratory (one lab manager and one safety officer). In addition, six staff members from Cohort I laboratories participated (four from the NRL, one from CHUK and one from CHUB) because of a need to replace SLMTA-trained staff lost due to turnover and transfers.

In March 2013, five additional district hospital laboratories (Bushenge, Kibagabaga, Ruhango, Ruhengeri and Rwamagana) were enrolled in Cohort III. Each laboratory provided three participants: one laboratory manager, one quality officer and one safety officer. In addition to these 15 participants, laboratories from previous cohorts sent 11 participants (five from the NRL, two from KMH, one from CHUK, one from CHUB, one from Kibungo and one from Nyagatare), again to replace trained staff who had left.

Audits

To evaluate progress, audits were conducted for all three cohorts using the SLIPTA checklist, before (baseline) and after (exit) SLMTA workshops. Depending on the audit scores, laboratories were awarded zero to five stars. A rating of zero stars was given for a score of < 55% (0–141 points), one star for 55% – 64% (142–166 points), two stars for 65% – 74% (167–192 points), three stars for 75% – 84% (193–218 points), four stars for 85% – 94% (219–243 points) and five stars for ≥ 95% (244–258 points).[10] Follow-up audits (performed from three to 18 months after the exit audits) were conducted for Cohorts I and II, but follow-up audits for Cohort III laboratories had not yet been completed at the time of the writing of this article. Cohort I laboratories received one follow-up audit, with the exception of NRL, which had four. In Cohort II, Byumba, Gihundwe and Gisenyi each had two follow-up audits, whereas Gihundwe and Nyagatare had three.

All audits for Cohort I were conducted by consultants from the American Society for Clinical Pathology (ASCP). ASCP consultants teamed with Rwanda SLMTA facilitators to conduct baseline and exit audits for Cohorts II and III, whilst EAPHLN auditors conducted follow-up audits for Cohort II. The Ministry of Health selected two high-performing laboratories from Cohort II for official SLIPTA audit by the African Society for Laboratory Medicine (ASLM), namely, Nyagatare Hospital Laboratory and Gihundwe Hospital Laboratory.

Mentorship and performance-based financing

Seventeen local mentors with advanced diplomas or bachelor's degrees received a two-day training in-country in March 2012 in order to facilitate the implementation of quality management systems in the laboratories. They were tasked with helping SLMTA participants in the implementation of improvement projects, in reviewing lessons learned during workshops and in closing gaps identified during the audits. These local mentors visited each laboratory for five days following each workshop. Additionally, for Cohort II, mentors (two from Rwanda, one from Uganda) with Master's degrees in microbiology spent two weeks per month in the laboratories from May 2012 to December 2013, overlapping with SLMTA implementation.

Cohort II laboratories also implemented performance-based financing, the first time such a model had been used with SLMTA. The performance-based financing model is a contractual approach stipulating that services and purchasing activities performed by health providers must be of good quality and compliant with standards. Linking financial incentives for the facility with results is designed to motivate healthcare providers to provide health services according to the qualities required by national norms and standards. A payment amount of $15 000 was allocated on a quarterly basis to each Cohort II laboratory with a score of 100% on the SLIPTA checklist. The incentive was discounted based on the SLIPTA audit score for laboratories not achieving a score of a 100%. For example, if a laboratory received a score of 70% on the SLIPTA checklist, it would receive a payment of 70% of $15 000, or $10 500. To incentivise continuous quality improvement, performance-based financing allowances were withheld if the laboratory's SLIPTA score dropped by ≥ 3 percentage points from its previous score or resulted in a lower star rating. The laboratory could use this incentive money to buy

commodities and conduct post-audit activities, gap analysis, workshops and employee-recognition activities.

Results

Cohort I

At the baseline audit for Cohort I, four laboratories had zero stars (CHUB, CHUK, NRL, KMH) and one laboratory (KFH) was at two stars (Figure 1a, Table 1). KFH is a private hospital laboratory and had been pursuing hospital accreditation actively for three years prior to enrolment in SLMTA. At the exit audit, one laboratory (KMH) received one star, two laboratories received two stars (CHUB, NRL) and two laboratories received three stars (CHUK, KFH). There was marked improvement in all laboratories, with median scores increasing from 43% to 73%. At the follow-up audit, one year after the exit audit, two laboratories earned three stars (CHUB, KFH) and three laboratories achieved four stars (CHUK, NRL, KMH).

Cohort II

In Cohort II, all laboratories received zero stars at the baseline audit (Figure 1b, Table 1). At the exit audit, three laboratories received two stars (Gihundwe, Gisenyi, Kibungo) and two laboratories received three stars (Byumba, Nyagatare). Median scores increased from 28% at baseline to 70% at the exit audit. At the first follow-up audit, three months after exit, one laboratory was at one star (Kibungo), three laboratories had earned three stars (Byumba, Gisenyi, Nyagatare) and one had earned four stars (Gihundwe). At the official SLIPTA audit conducted by ASLM in July 2013, five months after the first follow-up audit, Nyagatare Hospital Laboratory was awarded two stars and Gihundwe Hospital Laboratory three stars. Scores were somewhat lower (three percentage points for Nyagatare Hospital Laboratory and eight for Gihundwe Hospital Laboratory) than those received at the first follow-up audit. A second follow-up audit in November 2013 resulted in similar scores to the first follow-up, with the exception of Kibungo Hospital Laboratory, whose score increased 20 percentage points to 80% (Figure 1b).

Cohort III

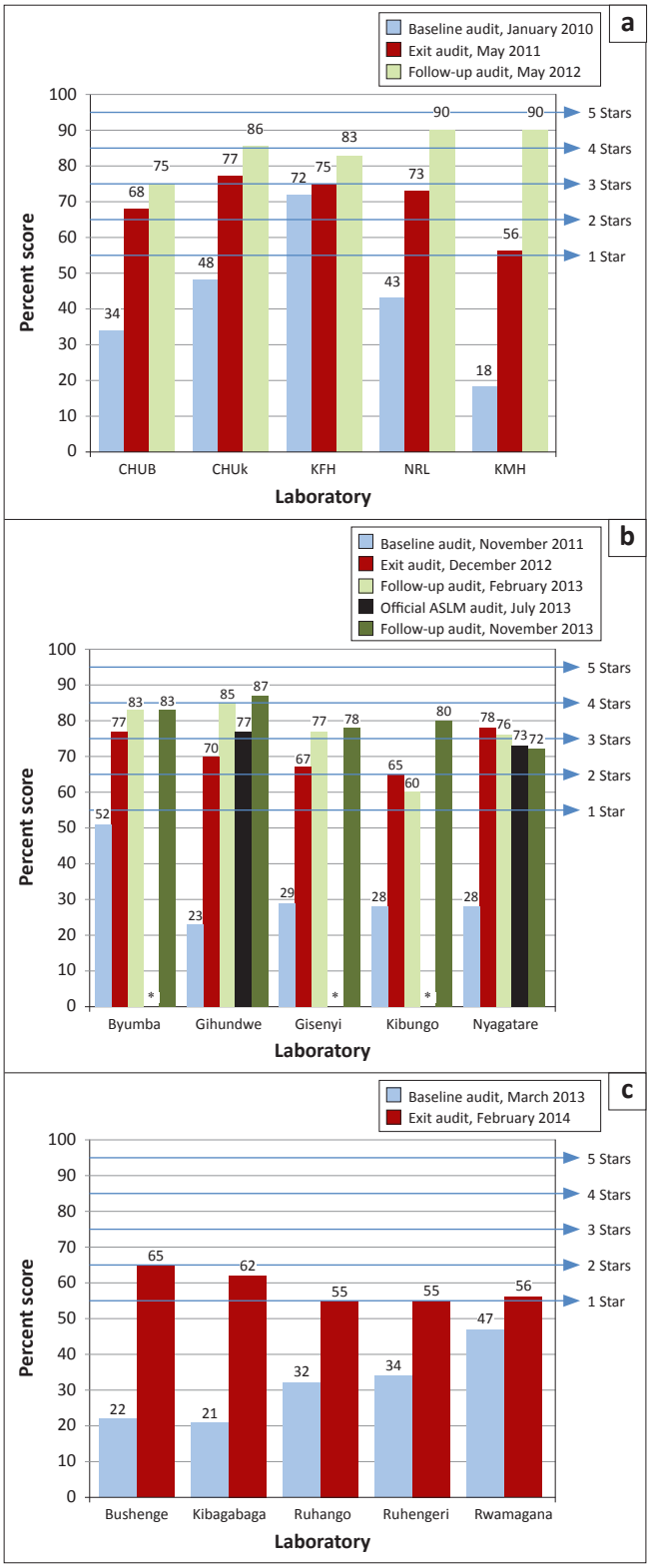
At the baseline audit for Cohort III, all five district hospital laboratories had zero-star ratings (Figure 1c, Table 1). At the exit audit, four laboratories received one star (Kibagabaga, Ruhango, Ruhengeri, Rwamagana) and one laboratory received two stars (Bushenge). Median scores increased from 32% at baseline to 56% at exit.

National reference laboratory

The NRL participated in six audits during the period of 2010 to 2013. The laboratory showed marked, though unsteady, improvements from 43% at baseline to 86% at the fourth follow-up audit nearly four years later. At the first follow-up audit in November 2011, the NRL received two stars, a score similar to that awarded at the exit audit six months earlier. At the second follow-up audit in May 2012, the NRL earned four stars, but at the third follow-up audit in February 2013, the NRL decreased slightly to a three-star rating (Figure 2).

Performance-based financing

Performance-based financing incentives of $75 000 were planned to be awarded to the five laboratories in Cohort II for each quarter. The maximum amount received in a quarter



SLMTA, Strengthening Laboratory Management Toward Accreditation; SLIPTA, Stepwise Laboratory Quality Improvement Towards Accreditation; CHUB, Centre Hospitalier Universitaire de Butare; CHUK, Centre Hospitalier Universitaire de Kigali; KFH, King Faisal Hospital; KMH, Kanombe Miltary Hospital; NRL, National Reference Laboratory; ASLM, African Society for Laboratory Medicine; *Audit not conducted.

FIGURE 1: Progress of SLMTA Cohorts I (a), II (b) and III (c) in Rwanda based on SLIPTA checklist scores.

TABLE 1: Cohort-level audit scores.

Cohort	Baseline audit		Exit audit		Median improvement from baseline to exit audit		1-year follow-up audit		Median improvement from exit to follow-up audit	
	Median %	Range	Median %	Range	Percentage Points	Range	Percentage Points	Range	Percentage Points	Range
Cohort I	43	18–72	73	56–77	30	3–38	86	75–90	9	7–34
Cohort II	28	23–52	70	65–78	38	25–50	80	72–87	11	6–17
Cohort III	32	21–47	56	55–65	23	9–43	-	-	-	-

was $13 050 by Gihundwe laboratory which scored 87% at their first follow-up audit. Two laboratories (Nyagatare and Kibungo) were not awarded incentives for one quarter because of a drop in star levels.

Discussion

Results of this study show substantial improvement in laboratories enrolled in SLMTA since 2010, as shown by star rating results. All but one of the 15 laboratories had a zero-star rating at the baseline audit, suggesting very low levels of quality management. At the conclusion of the SLMTA training programme, every laboratory had achieved at least one star, with four laboratories obtaining three or more stars. Furthermore, laboratories continued to improve after the end of the SLMTA programme, with nine of the 10 laboratories conducting follow-up audits achieving three or more stars.

Establishing a stepwise approach in order to guide laboratories in a gradual improvement process, as well as offering evaluations that demonstrate progress at each level, is a dynamic way of implementing quality laboratory standards in developing countries.[11] Improvements resulting from SLMTA implementation have been observed elsewhere; however, Rwanda's results are somewhat higher than what is typically found. For example, amongst 321 laboratories worldwide that have completed the SLMTA training, nearly one third (29%) remained at zero stars after SLMTA implementation, with a mean score increase of 23 percentage points, compared with Rwanda's results of all laboratories achieving at least one star and a median improvement of 34 percentage points.[12]

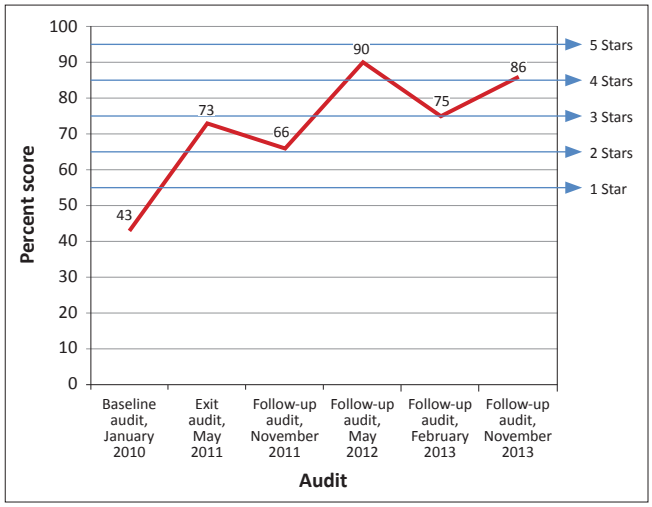


FIGURE 2: Progress of the National Reference Laboratory (NRL) from 2010–2013, based on Stepwise Laboratory Quality Improvement Toward Accreditation (SLIPTA) checklist scores.

For system-wide improvement, the Rwandan government encourages collecting and using laboratory data for advocacy; programmatic data are now used in developing policies aimed at improving quality services. For example, a cross-cutting problem in many laboratories in Rwanda has been service interruptions as a result of stockouts and equipment breakdowns. To address this problem, CHUK conducted an improvement project between its second and third SLMTA workshops which focused on calculating the financial impact of service interruption. From July to September 2010, stockouts and equipment breakdowns prevented the laboratory from performing 6486 tests, which were referred to private laboratories. The laboratory estimated that, if performed, the tests would have generated revenue of $14 308. In contrast, the funds needed to purchase the necessary reagents and maintain equipment were estimated at $5711, resulting in a net loss of $8597 in potential income to the hospital. After reviewing these findings, hospital senior management agreed to purchase a back-up clinical chemistry analyser and signed a maintenance agreement with laboratory equipment manufacturers with the aim of ensuring continuity of laboratory services.

Sustainability is a critical issue for SLMTA and other improvement programmes. Data from Cohorts I and II show that not only were the gains achieved through SLMTA implementation sustained a year after completion of the training programme, but they continued to increase a median of 10 additional percentage points. The KMH laboratory in Cohort I showed the greatest post-SLMTA improvement, with scores increasing from 56% (one star) at the exit audit to 90% (four stars) one year later. This laboratory had the lowest baseline score amongst all laboratories in Rwanda's SLMTA programme to date, yet has now earned the highest follow-up score in the country's programme. Staff at KMH attributed this remarkable achievement to high levels of commitment, team work and hospital management support of and direct involvement in the quality improvement effort. The KMH staff's pride in their accomplishments is highlighted by the fact that in May 2012 they changed their name from Kanombe Military Hospital, which was linked to their military camp, to Rwanda Military Hospital (RMH). They also began to expand their testing capacity by introducing new services, including molecular biology, enzyme-linked immunosorbent assays and systematic bacteriology culture, as well as building a new laboratory infrastructure in their preparation to transition into a referral hospital.

Overall, Cohort II showed the greatest improvement of the three cohorts, with a median improvement of 38 percentage

points from baseline to exit and an additional 11 percentage points a year later (Table 1). Several factors may help to explain these successes. Firstly, these laboratories received additional funding from the World Bank's EAPHLN in order to support improvement projects and other elements of quality management systems, including building infrastructure and purchasing back-up equipment and safety items such as first aid kits, spill kits and eye wash stations. Secondly, these laboratories had the benefit of extensive on-site expert mentorship to assist with improvement projects and programme implementation. However, Cohort II was not without challenges. For example, Nyagatare Hospital Laboratory, which was one of the two laboratories audited by ASLM, lost their quality officer (September 2012) and laboratory manager (August 2013); despite sending replacements to be trained along with Cohort III laboratories, their scores declined steadily after the exit audit, dropping from 78% at exit to 72% at the second follow-up audit 11 months later (Figure 1b).

Cohort II also implemented an innovative performance-based financing incentive system. Performance-based financing has been used by many development organisations to ensure greater accountability and to improve the efficiency of funded programmes.[13] Haiti was the first low-income country in which health service providers were remunerated according to their performance.[14] In Cambodia, performance-based financing was applied to the public sector; despite promising results, however, it did not materialise into a national policy.[15] Rwanda has been on the cutting edge of this approach, implementing performance-based financing in several sectors since 2002.[16,17,18]

NRL staff participated extensively in all three cohorts, as this laboratory is expected to provide leadership and guidance on quality management systems for Rwanda's entire laboratory network. Also, as part of the EAPHLN, the NRL was in a unique position to monitor the progress and challenges of SLMTA implementation in the network laboratories.

Multiple factors may have contributed to variability in audit scores for NRL. As the country's only national reference laboratory, the NRL provides a large proportion of services and routine testing in the country. This creates a heavy and fluctuating workload for the staff and the staff may not consistently prioritise quality improvement activities. Variability in scores could also reflect the senior management's lack of focus on the accreditation preparation process. To overcome these challenges, there has been renewed commitment by senior management to focus on strengthening the laboratory systems at the NRL. In March 2013, a laboratory technical working group was launched with an accreditation subcommittee. The NRL is also undertaking extensive decentralisation to reduce routine testing and workloads, enrolling in external quality assessment programmes and supporting mentorship in all sections of the laboratory. The Rwanda Ministry of Health is forging ahead with its goal of implementing SLMTA in the remaining district hospital laboratories and ensuring that laboratories sustain momentum after programme completion by integrating continuous improvement into routine management.

Conclusion

In Rwanda, laboratories enrolled in the SLMTA programme demonstrated measurable improvements. Performance-based financing, intensive monitoring and supplementary financial resources may have contributed to gains in Cohort II laboratories. Strengthening of an effective laboratory technical working group is needed to oversee the accreditation preparation process, mobilise resources and further develop the plan outlined by the Ministry of Health for long-term sustainability of quality laboratory systems. Expanding the use of performance-based financing to incentivise the quality improvement process in Rwanda may contribute to accreditation readiness.

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Competing interests

The authors declare that they have no financial or personal relationship(s) that may have inappropriately influenced them in writing this article.

Authors' contributions

I.N. (Rwanda Biomedical Center/National Reference Laboratory) and W.G. (CDC, Rwanda) were the study leaders. J.B.M., I.N., E.N., C.M.M. and S.S. (all Rwanda Biomedical Center/National Reference Laboratory), as well as W.G., conceived and designed the study. M.K.L. (ASCP), J.B.G. (Rwanda Military Hospital) and C.K. (SPIU/Ministry of Health, Kenya), as well as E.R., I.N., S.S. and J.S. (all Rwanda Biomedical Center/National Reference Laboratory) collected the data. I.N., W.G. and G.A.D. (CDC, Rwanda) analysed the data; and I.N., C.M.M., E.N., W.G. and J.B.G. wrote the manuscript.

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Evolution of Couples' Voluntary Counseling and Testing for HIV in Rwanda: From Research to Public Health Practice

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Background: Couples' voluntary HIV counseling and testing (CVCT) is a WHO-recommended intervention for prevention of heterosexual HIV transmission which very few African couples have received. We report the successful nationwide implementation of CVCT in Rwanda.

Methods: From 1988 to 1994 in Rwanda, pregnant and postpartum women were tested for HIV and requested testing for their husbands. Partner testing was associated with more condom use and lower HIV and sexually transmitted infection rates, particularly among HIV-discordant couples. After the 1994 genocide, the research team continued to refine CVCT procedures in Zambia. These were reintroduced to Rwanda in 2001 and continually tested and improved. In 2003, the Government of Rwanda (GoR) established targets for partner testing among pregnant women, with the proportion rising from 16% in 2003 to 84% in 2008 as the prevention of mother-to-child transmission program expanded to >400 clinics. In 2009, the GoR adopted joint posttest counseling procedures, and in 2010 a quarterly follow-up program for discordant couples was established in government clinics with training and technical assistance. An estimated 80%–90% of Rwandan couples have now been jointly counseled and tested resulting in prevention of >70% of new HIV infections.

Conclusions: Rwanda is the first African country to have established CVCT as standard of care in antenatal care. More than 20 countries have sent providers to Rwanda for CVCT training. To duplicate Rwanda's success, training and technical assistance must be part of a coordinated effort to set national targets, timelines, indicators, and budgets. Governments, bilateral, and multilateral funding agencies must jointly prioritize CVCT for prevention of new HIV infections.

Key Words: couples' HIV testing, Rwanda, implementing WHO guidelines

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INTRODUCTION

Worldwide, 35.3 million adults and children are living with HIV as of 2012.[1] Approximately, 70% of these individuals reside in sub-Saharan Africa where most new adult infections occur through heterosexual transmission.[1] In countries with HIV prevalence >10% among adults, 1 in 4 cohabiting couples and half of HIV-affected couples are HIV discordant with 1 HIV-infected (HIV+) and 1 HIV-uninfected (HIV−) partner.[2–4] Consequently, cohabiting couples represent a large, high-risk population for HIV.[5]

Couples' voluntary HIV counseling and testing (CVCT) is an effective intervention for prevention of heterosexual HIV transmission in sub-Saharan Africa,[3,6–11] particularly in Rwanda where ≥90% of new infections occur in cohabiting couples.[5,12–15] CVCT provides both partners with the opportunity to share their HIV test results, jointly address issues related to HIV transmission and family planning, and support each other if one or both are infected.[16–20] CVCT is also associated with an increased uptake of interventions to reduce mother-to-child transmission[21,22]and with a lower risk of HIV infection in infants born to HIV+ mothers.[7,23,24]

Despite increased recognition of the effectiveness of CVCT, very few couples in sub-Saharan Africa have the opportunity to be counseled and tested together or to mutually disclose their test results. In fact, most adults are either unaware of their own HIV status, that of their partner, or both,[18,25–27] and in many cases adults do not know that it is possible to have a long-standing partner with a different HIV status.[28,29] To our knowledge, Rwanda is the only country in Africa that has successfully implemented CVCT as a national

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standard, with approximately 88%–90% of married men and women aged 25–29 tested as a couple.[30] This article traces the evolution of CVCT in Rwanda from research findings to a nationwide evidence-based intervention and a social norm.

Coauthors and Organizations

Projet San Francisco (PSF) is a research organization established in Kigali in 1986 as a collaborative program with the Ministry of Health (MoH) (E.K., J.M., R.B, K.K., B.B.-H). Together with its sister organization, the Zambia Emory HIV Research Project (ZEHRP), it forms the Rwanda Zambia HIV Research Group (RZHRG), headquartered at Emory University (K.M.W, A.T., S.A.). The Rwanda Biomedical Center (RBC) of the MoH is an agency that incorporates what was previously the Treatment and Research AIDS Center (TRAC), the National Reference Laboratory (NRL), and the National TB and malaria control programs (S.N., P.M., E.R.). The US Centers for Disease Control and Prevention (CDC) office in Rwanda funded the training and technical assistance components of nationwide CVCT implementation (FN, PR).

First Evidence of CVCT As an Effective Intervention for HIV Prevention in Rwanda, 1986–1994

In 1986, HIV testing in Rwanda was performed for surveillance purposes at the National AIDS Control Program, and for blood screening at the National Blood Transfusion Center.

Between October 1986 and March 1987, HIV screening (enzyme-linked immunosorbent assay with Western blot confirmation) was provided to a consecutive sample of 3702 young women aged 18–35 years attending the antenatal care (ANC) and pediatric clinics at the Central Hospital of Kigali; the prevalence of HIV was 29%.[31] In March–August 1988, with NIH funding to study the incidence, predictors, and natural history of HIV (NIH AI23980), PSF enrolled a subset of women (460 HIV+ and 998 HIV−) for a prospective cohort study[32] and many requested HIV testing be provided to spouses. More than 25% of male partners sought testing when offered: 15% of couples had discordant HIV results, 20% were concordant positive, and the remaining 65% were concordant negative. After 1 year of follow-up, condom use in discordant couples increased from 4% to 57%,[14] and the rate of HIV seroconversion among women with untested male partners was more than twice that for women whose partners were tested.[13] Partner testing was also associated with a significant decrease in gonorrhea rates among HIV+ women. Pregnancy incidence decreased among all women when hormonal contraceptives were provided at the research clinic.[33,34] When men and women were counseled separately, at times individuals did not disclose their results to their partners or disclosed inaccurate results.[15,35] This posed a particular problem for discordant couples, and for concordant HIV+ couples in which each told the other partner they were HIV−. To optimize prevention, PSF developed procedures for joint pretest and posttest counseling.[36]

After the evidence of the potential impact of the CVCT intervention on prevention of HIV, sexually transmitted infections, and unplanned pregnancy, additional funding was sought to study behavioral, clinical, virologic, immunologic, and immunogenetic predictors of heterosexual transmission from man to woman and woman to man, in both donor and recipient in discordant couples (NIH AI40951). A testing center for couples was established, and outreach and promotion strategies publicized the services. By April 1994, the center received 10–15 couples/d and 241 discordant couples had enrolled in a cohort study. Unfortunately, during the genocide against the Tutsi in April–July 1994, all CVCT activities were interrupted, most PSF staff and participants were killed or fled, and the project relocated to Zambia.

Nine Rwandan PSF staff and their families came to Lusaka, Zambia's capital, to assist with the relocation of the NIH-funded studies of discordant couples. Between 1994 and 1997, these staff and their Zambian counterparts established a CVCT program and continued to refine procedures for recruiting couples for joint testing and following HIV-discordant couples.[37,38] In 1997 when the situation in Rwanda had calmed, Rwandan staff wanting to return were assisted to do so.

Demonstration Projects and Refinement of CVCT Procedures in Postgenocide Rwanda, 1997–2002

In 1997, a grant was obtained from United Nations Population Fund (UNPF) to offer CVCT alongside family planning services to Kigali couples. Using procedures honed in Lusaka, when couples arrived at PSF, they were first received in a group discussion session led by a counselor. Each couple then participated together in a joint confidential pretest counseling session where they had an opportunity to speak freely and ask sensitive questions that could not be addressed in group discussion. Afterward, the couple went for phlebotomy, which included HIV rapid testing (available in 1995 and first implemented at ZEHRP[37,38]) and rapid plasma reagin syphilis serology. Same-day test results were provided during joint posttest counseling. Both partners were together throughout the process, and services were provided free of charge with transport reimbursement, lunch, and child care. By 1999, the UNFPA-funded program had served >5000 couples.

In 2001, RZHRG was awarded a World AIDS Foundation (WAF) grant to explore the feasibility of establishing CVCT in government ANC clinics in Kigali and Lusaka. At that time, only 2 health centers in Kigali were offering HIV testing in prevention of mother-to-child transmission (PMTCT) programs.[39] Staff in these 2 centers were trained by PSF counselors and distributed written invitations to ANC clients to return with spouses for weekend CVCT programs. Between March and December 2001, 984 women received individual HIV testing and 956 women received CVCT. Corresponding numbers in Lusaka were 1022 and 663.[40]

Demand Creation and Development of Best Practices for CVCT, 2003–2008

A US National Institutes of Mental Health grant (MH66767) allowed PSF to study CVCT obstacles at the

policy, provider, and client levels and to develop best practices in promotion and provision of CVCT. A household survey in 2003 confirmed that though most adults wanted to be tested with their partners, many thought CVCT was available at public facilities (which was not yet the case), and only 25% knew CVCT reduced HIV transmission within marriage.[41]

To coordinate demand and supply, a promotional strategy to invite couples for CVCT was developed and tested with a neighborhood randomized controlled trial in Kigali and Lusaka.[42–44] Social Norms Theory highlights the role of community and peer influence in changing health behaviors, and studies have shown that normalizing behaviors like HIV testing through community promotions can decrease stigma and increase uptake.[45,46] Influential network leaders (INLs) were selected from the health care, religious, nongovernmental/community-based, and private sectors. Each INL nominated influential network agents (INAs) and supported the INA's promotional efforts through public endorsements of CVCT. INAs received a 4-day training including observation of the CVCT process and demonstration of promotion among friends, family, workmates, church members, and the community. Performance-based pay was linked to the number of couples presenting an INA invitation at CVCT. This model was successful, particularly when invitations were distributed to the homes of individuals known personally to the INA, accompanied by an INL public endorsement, and with the availability of a mobile testing unit.[42,43]

Between 2003 and 2008, 41,582 couples were tested together including 9099 boy/girlfriend or fiancée noncohabiting couples and 32,483 cohabiting couples. This corresponded to 15% of couples in Kigali[47] and set the stage for diffusion of CVCT as a norm in both cohabiting and premarital couples.[48,49]

The prevalence of HIV infection from 2003 to 2008 was 10.2% among women and 5.9% among men in noncohabiting couples, and 14.3% among women and 13.4% among men in cohabiting couples. These prevalence rates were higher than those estimated by the Rwanda Demographic Health Survey in 2005, which showed the proportion of people infected by HIV in Kigali to be 8.0% of women and 5.2% of men.[47] This suggests that couples requesting CVCT services at PSF stand-alone centers may have been at higher risk than the general population.

During this time, counselors from PSF and the sister site in Zambia joined the US CDC and the Liverpool School of Tropical Medicine to develop training materials for couples' HIV counselors, promoters, and program managers. These were finalized and posted on the US CDC website in late 2007[21] (http://www.cdc.gov/globalaids/resources/prevention/chct.html).

National Campaign for Partner Testing in ANC, 2003–2008

In November 2003, PSF and the MoH organized a consensus conference to endorse CVCT services. The conference was opened by the President of Rwanda, His Excellency Paul Kagame. Attendees included government ministers, representatives from US and European embassies, and key stakeholders involved in implementation of HIV prevention services including UN agencies, multilateral and bilateral organizations, nongovernmental organizations, district hospitals, and representatives of health centers. This conference culminated in the launching of a "10 by 10" campaign to test 10% of Rwandan couples by 2010. As the timing coincided with the expansion of HIV testing for pregnant women in PMTCT programs and feasibility of partner testing had been confirmed in Kigali, the MoH and the National AIDS Control Program gave priority to partner testing in ANC.

In 2003, when the national PMTCT campaign was launched, only 53 of the 442 government health centers nationwide offered voluntary testing and counseling services. That year nearly 35,000 pregnant women were tested for HIV and 16% of their male partners also came to the clinic for HIV testing. Promotional efforts were undertaken by the network of community health workers (CHWs) known in Rwanda as "Animateurs de Santé." These are volunteers chosen by their communities to inform the population about disease prevention, and they work under the supervision of a health center. Nearly 45,000 CHWs were mobilized with support from local political leaders and staff from health centers. These CHWs received promotional training (adapted from the INA training developed during PSF research described above), thereafter visiting homes of pregnant women to encourage them and their husbands to seek testing. Monthly meetings were held at health centers to review progress and share best practices for promotion. Throughout the campaign, local and district political leaders were also actively involved in promoting ANC testing with male partner involvement at community gatherings, particularly on the community workday "Umuganda," the last Saturday of every month. Radio announcements were also effective in spreading the message as only 1 language is spoken throughout Rwanda and radio stations broadcast nationwide.

These promotional efforts resulted in a steady increase of the uptake of HIV testing by pregnant women and their partners. The proportion of male partners tested in ANC increased to 33% after 2 years and 66% after 4 years (national program data, Fig. 1). By the end of 2008, 341 health centers were offering counseling and testing services to pregnant women. That year 300,000 pregnant women were tested of whom 78% had male partners who also tested.

During the first 5 years of the PMTCT program, ANC attendees and their partners were counseled and tested separately in government clinics. This practice arose in part from logistics: women were tested during their first ANC visit and given invitations to take home to their partners who came at a later date. In addition, data collection tools included sensitive sexual history questions that were challenging to ask when husband and wife were together. Lastly, there was confusion about the role of confidentiality and a widespread assumption that husband and wife would "work it out on their own." Although couples were encouraged to mutually disclose their serostatus, the frequency of disclosure was not documented.

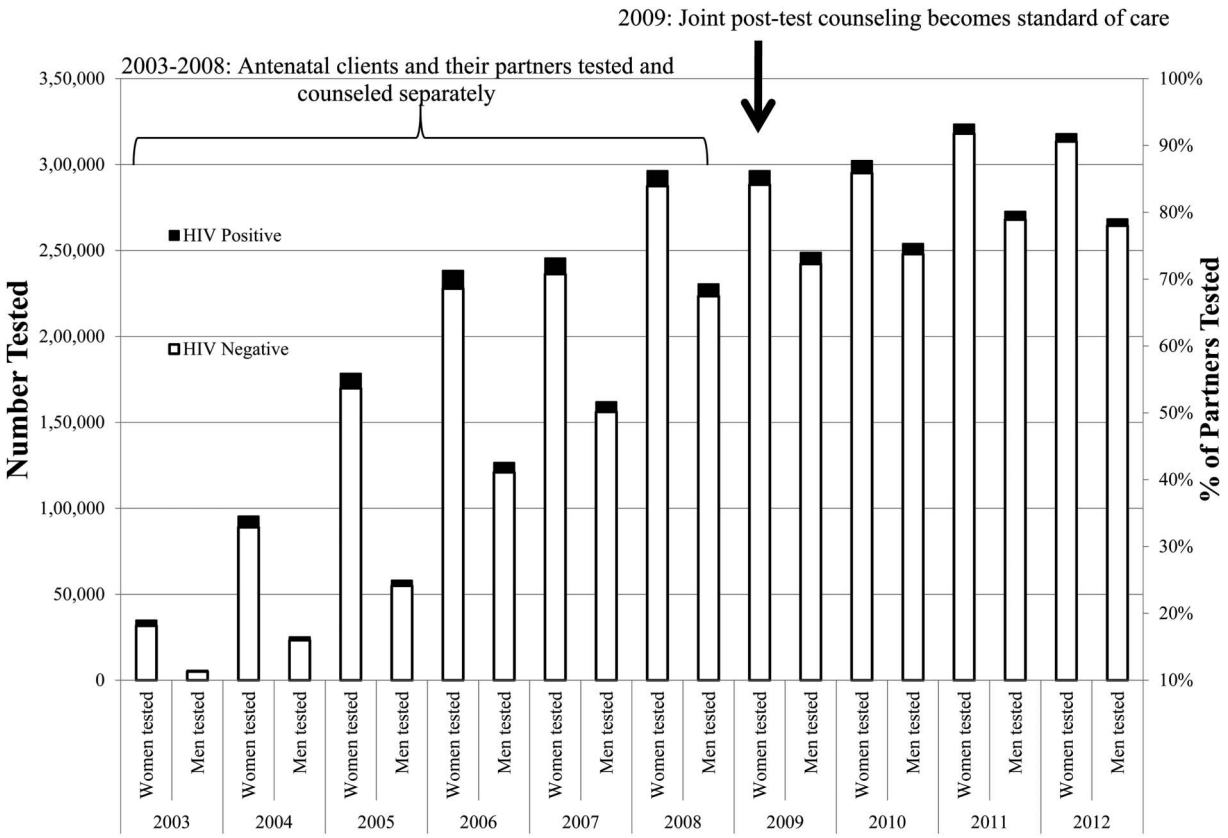

FIGURE 1. Ten years of nationwide HIV testing in antenatal clinics, 2003–2012.

Nationwide Transition to Joint Posttest Counseling and Enrollment of Discordant Couples in Quarterly Follow-Up, 2009–2014

Rwanda adopted new guidelines in 2009 which specified that pregnant women and their partners should be jointly posttest counseled with mutual disclosure of HIV results, as was specified in CDC counselor training guidelines[50] and later endorsed in WHO guidelines.[51] To pilot this procedure, PSF counselors trained and supported government staff in several clinics in Kigali to provide weekend CVCT (as had been done in the WAF study in 2001 described above), with the goal of transitioning the procedures to weekday ANC services. According to the performance-based financing system,[52,53] the MoH paid clinics for services rendered. It quickly became clear to clinic managers and staff that counseling 2 people jointly required far less time than counseling them as individuals, and that CVCT was thus time and cost saving. The additional benefit—much appreciated by counselors—was that difficulties with couples who did not disclose or disclosed inaccurately could be avoided. Figure 2 shows the rapid transition from weekend to weekday CVCT in these Kigali clinics during the last quarter of 2008.

It became apparent during the pilot that government counselors required new skills to comfortably counsel couples together effectively, particularly those in whom HIV results were discordant. The MoH requested that PSF provides technical assistance and training on the joint counseling and testing model for health care providers nationwide. With funding from CDC (U2G-PS-1839), training modules were also developed for clinic managers, laboratory technicians, promotion managers, and data managers. The content of each training module was tailored to each health professional category involved in the program. Training for counselors focused on the skills required for the counseling of a couple; training of clinic managers encompassed the management of the CVCT program in the health care facility and advocacy of the program with community stakeholders; promotion managers were prepared to train CHWs and to coordinate outreach activities for CVCT promotions; laboratory technicians were trained specifically on HIV testing algorithm adapted for couples (specifically the addition of confirmatory testing for all those HIV+ on screening and their partners),[18] whereas data managers were trained on CVCT reporting, monitoring, and evaluation. Indicators reported to RBC included number of couples tested by serostatus and indeterminate test results.

In 2010, quarterly follow-up of discordant couples in government clinics was added to the counselors' training manual. Follow-up procedures and longitudinal data collection tools adapted from research protocols were streamlined for program use to record HIV test result for the HIV− (or seroconverting) partner, pregnancy status and contraceptive use, and antiretroviral therapy (ART) use for the HIV+ partner. These have now been implemented in hundreds of government clinics following approximately 40,000 discordant couples.

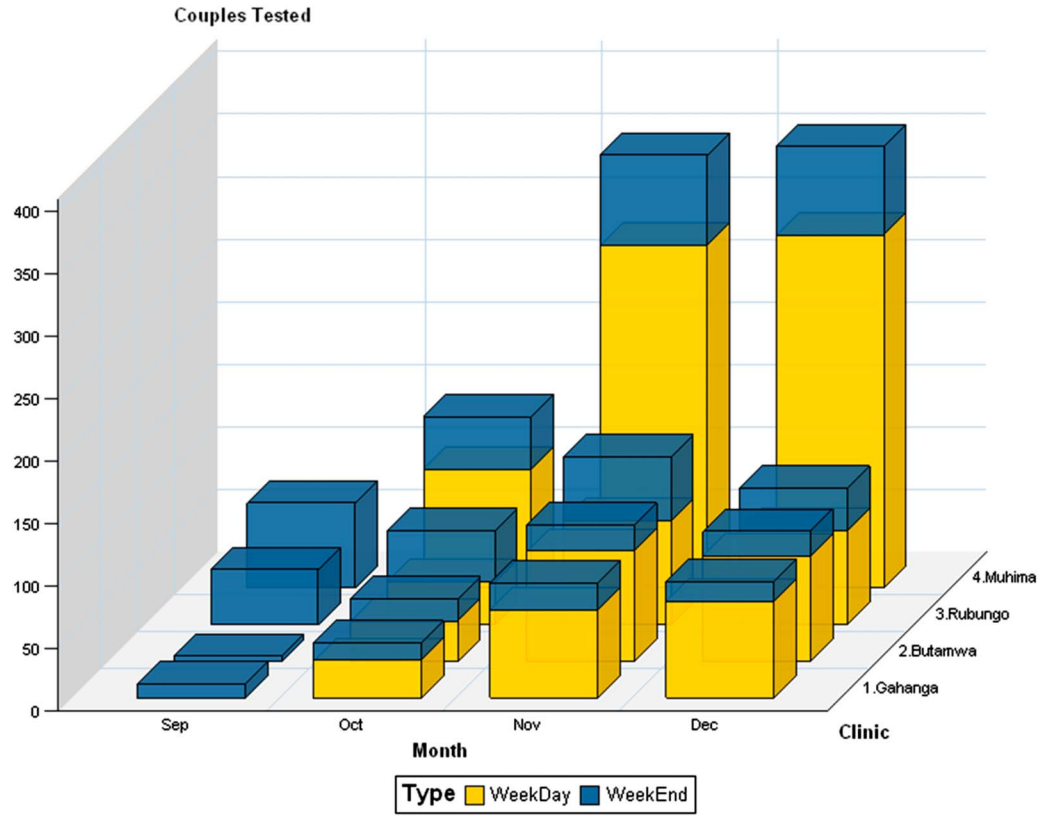

FIGURE 2. Transition from weekend to weekday CVCT integrated in selected Kigali ANC clinics, October–December 2008.

Between 2009 and 2013, PSF trained more than 2500 health providers, 77% of whom were counselors, 7% data managers, 6% laboratory technicians, 6% promotion managers, and 4% clinic managers (Table 1).

The number of health care facilities offering voluntary testing and counseling services in Rwanda increased to >400 in 2012. During this period, the proportion of pregnant women testing with husbands increased more than five-fold, from 16% to 84% (Fig. 1). This proportion plateaued in 2009, probably due to single mothers and men without time or inclination to accompany their spouses to ANC.

DISCUSSION

In this article, we describe the steps leading to the successful nationwide implementation of CVCT—an evidence-based, feasible, affordable, and sustainable program that prevents an estimated >70% of incident HIV infections in Rwanda.[5,12] To our knowledge, Rwanda is the first country to establish CVCT as a norm in ANC and reach an estimated 90% of couples. We discuss lessons learned and compare Rwanda with other African countries, notably Zambia where many of the same CVCT research and advocacy activities have taken place but successful demonstration projects have not led to a national program.

An important aspect of Rwanda's success has been government support and collegial relationships between research, government, and implementation sectors. These were vital to coordinating policy, funding, promotion, and service provision. Rwanda's small size, dense population, good transport and communication infrastructure, and homogeneous language have also facilitated rapid dissemination of CVCT.

TABLE 1. Nationwide Training of CVCT Teams in Government Clinics

	CVCT Counseling	Refresher CVCT	Discordant Couple Follow-Up	CVCT & Discordant Couple Follow-Up	Data Manager	Health Center Manager	Laboratory Technician	Promoter Manager	Total Trained Per Year
2009	106	0	0	0	0	0	0	0	106
2010	93	0	84	130	99	52	50	97	605
2011	24	182	0	199	41	45	74	33	598
2012	0	143	0	686	0	0	0	13	842
2013	0	134	5	189	28	17	18	0	391
Total	223	459	89	1204	168	114	142	143	2542

The support of local leaders and the active involvement of CHWs and health care providers were critical for demand creation and were leveraged by Performance-Based Financing and Community Health Insurance schemes in the health sector. The timing of the MoH's commitment to CVCT was fortuitous as it coincided with national PMTCT expansion.

Zambia and Rwanda have similar populations, but Zambia is 15 times larger and has five major language groups with 73 dialects. Knowledge of HIV discordancy is far lower in Zambia versus Rwanda,[41] and also low in South Africa.[28] As a result, many do not disclose their HIV test results to partners and husbands often assume that their wife's test result from ANC must be the same as their own.[15,35]

In Zambia, CVCT demonstration projects funded by the UK Department for International Development (DFID), the Canadian International Development Agency (CIDA), and the US CDC used the same procedures as Rwanda, including advocacy at national, provincial, district, and community levels; community- and clinic-based promotions incentivized with performance-based pay; transport reimbursement for couples (a necessary component in early stages, and one endorsed by both sides of a USAID-World Bank debate on the use of incentives for HIV prevention[54]); and weekend services in government clinics. These demonstration projects provided CVCT services to over >250,000 of Zambia's 2.5–3.0 million couples in 7 cities and 26 underserved districts in 8 years. In some cities, CVCT uptake increased from <3% to 25% of ANC clients tested with partners. Unfortunately, this plateaued in 2014, and many HIV implementing partners continue to offer only individual testing.

Separate HIV testing of women and their partners is a missed prevention opportunity, and it illustrates how a critical procedural component can be overlooked when parties with different deliverables are involved. It is notable that to this day, international agencies tasked with HIV prevention programs in Africa still do not include CVCT among their indicators although prevention of HIV in women of childbearing age is the first of 4 prongs of PMTCT cited by WHO/UNAIDS.[42] In Zambia, virus sequencing confirms that 9 of the 10 new infections in women come from their spouses.[55] Testing pregnant women with partners at the first ANC visit has the advantage of identifying discordant couples and thus likely preventing both heterosexual and perinatal transmission,[56] unlike repeat maternal testing during pregnancy and postpartum[57,58] which, without CVCT, measures—but does not prevent—incident maternal HIV.

The recognition of discordant couples has led to investigations of behavioral, clinical, virologic, immunologic, and immunogenetic correlates of male-to-female and female-to-male transmission. Investigators have used CVCT to identify discordant couples for clinical trials of biomedical interventions such as ART, treatment-as-prevention (TasP), ART-containing vaginal microbicides, and pre-exposure prophylaxis. However, these studies did not report the prevention impact of the recruitment step—CVCT—which in observational studies reduced incidence from 10% to 11% in couples who did not know their results[59] to <3% in jointly counseled couples. CVCT thus prevented a large number of new infections before ART-based prevention was offered. The residual impact of ART-based regimens reduced incidence from 2% to 3% to close to zero among adherent participants.[60–62] Recent trials of "population TasP" have also not listed CVCT among the standard-of-care prevention services in study protocols,[63] even in home-based testing.[64] Demographic and Health Surveys-derived estimates show that most new infections occur in cohabiting couples,[5,12] and the consensus is that joint testing leads to reduced risk. CVCT should be prioritized rather than remaining an unmeasured component of individual HIV counseling and testing, which is framed as a case detection exercise that receives <5% international funding.[65]

Since 2013, the WHO recommended treating all HIV+ people in discordant partnerships with antiretroviral drugs to prevent transmission to their partners.[66] TasP among discordant couples cannot reach a meaningful number of couples until CVCT is effectively promoted and adopted as policy in HIV prevention programs, with adequate funding secured for its implementation. The prevention impact of CVCT is considerable without ART and given the low cost, CVCT can be implemented in areas without ART programs. Although TasP is available to many in Rwanda, it is much harder to access in southern African countries with similar per capita incomes and expenditures on health but much higher HIV prevalence rates, larger geographic areas, and multilingual populations.

Outside Rwanda, fewer than 10% of African couples are aware of their joint serostatus and this must be the first priority. International and national stakeholders must establish targets, timelines, and budgets for nationwide implementation of CVCT and look to Rwanda and to successful demonstration projects as models.

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POLICY FORUM

Transitioning to Country Ownership of HIV Programs in Rwanda

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Abbreviations: ART, antiretroviral therapy; CD4, cluster of differentiation 4; CDC, Centers for Disease Control and Prevention; CHW, community health worker; DHS, Demographic and Health Survey; FY, Fiscal Year; Global Fund, Global Fund for AIDS, Tuberculosis and Malaria; GOR, Government of

Summary Points

- Funding from the United States President's Emergency Plan for AIDS Relief (PEPFAR) program in 2004 significantly bolstered Rwanda's ability to develop a national HIV program with implementing partners.
- In 2009, after 5 years of expanding HIV services to achieve universal access to antiretroviral treatment, Rwanda and PEPFAR embarked on a sustainability and country ownership phase of the AIDS response.
- Commitment to the following seven principles helped to create a foundation for successful HIV program management transition from implementing nongovernmental partners to management by Rwanda: a political context of integration and decentralization, ownership through national coordination, participation and partnership, equity, efficiency, accountability, and integration of HIV care to strengthen the entire health system.

Introduction

An objective of development aid is to increase the capacity of recipient countries until they no longer require foreign assistance. Ideally, partners accompany host countries in this development journey by progressively transferring management skills and technical expertise to promote sustainability of country ownership of programs [1,2]. Reviews of donor-funded health programs have highlighted integration into existing government health systems as key to enabling sustainability [3–6]. However, there are few published analyses of how public health programs are transitioned from donor to host country management [2,7].

Rwanda; HHS, Department of Health and Human Services; ICAP, International Center for AIDS Care and Treatment Programs; MOH, Ministry of Health; NGO, nongovernmental organization; PEPFAR, United States President's Emergency Plan for AIDS Relief; PLWH, people living with HIV; PMTCT, Prevention of Mother to Child HIV Transmission; TB, tuberculosis; USD, United States dollars; USG, United States government.

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As defined through its national policy, *Vision 2020*, Rwanda has committed to reducing its dependence on external aid [8]. In response to the growing AIDS crisis, Rwanda advocated for increasing resources from bilateral, multilateral, and civil society organizations to combat HIV [9,10]. In 2003, the World Bank and the Global Fund for AIDS, Tuberculosis and Malaria (Global Fund) were among the first contributors to the AIDS response in Rwanda [8–10]. The launch of the US President's Emergency Plan for AIDS Relief (PEPFAR) program in 2004 dramatically increased the funding available to support HIV programs in Rwanda (Fig 1). PEPFAR provided 989.7 million US dollars (USD) from 2004 to 2013, and the Global Fund provided 529.2 million USD from 2003 to 2013 [9–12].

This article describes key principles that allowed for the successful transition of HIV program ownership from the donor-led agencies to Rwanda.

Launching National Scale-up for HIV Care in Rwanda

Through PEPFAR, the US government (USG) developed partnerships with the Government of Rwanda (GOR) for the national AIDS response. Six US agencies managed PEPFAR funds in Rwanda and supported national HIV scale-up programming; the Centers for Disease Control and Prevention (CDC) oversaw in-country implementation of Rwanda's national HIV program on behalf of the involved Department of Health and Human Services (HHS) agencies. This partnership helped to scale up a national emergency response to the HIV epidemic. Within 5 years, Rwanda's national HIV program achieved near-universal access to HIV prevention, care, and treatment (Table 1). Rwanda's decentralized health sector, as well as its

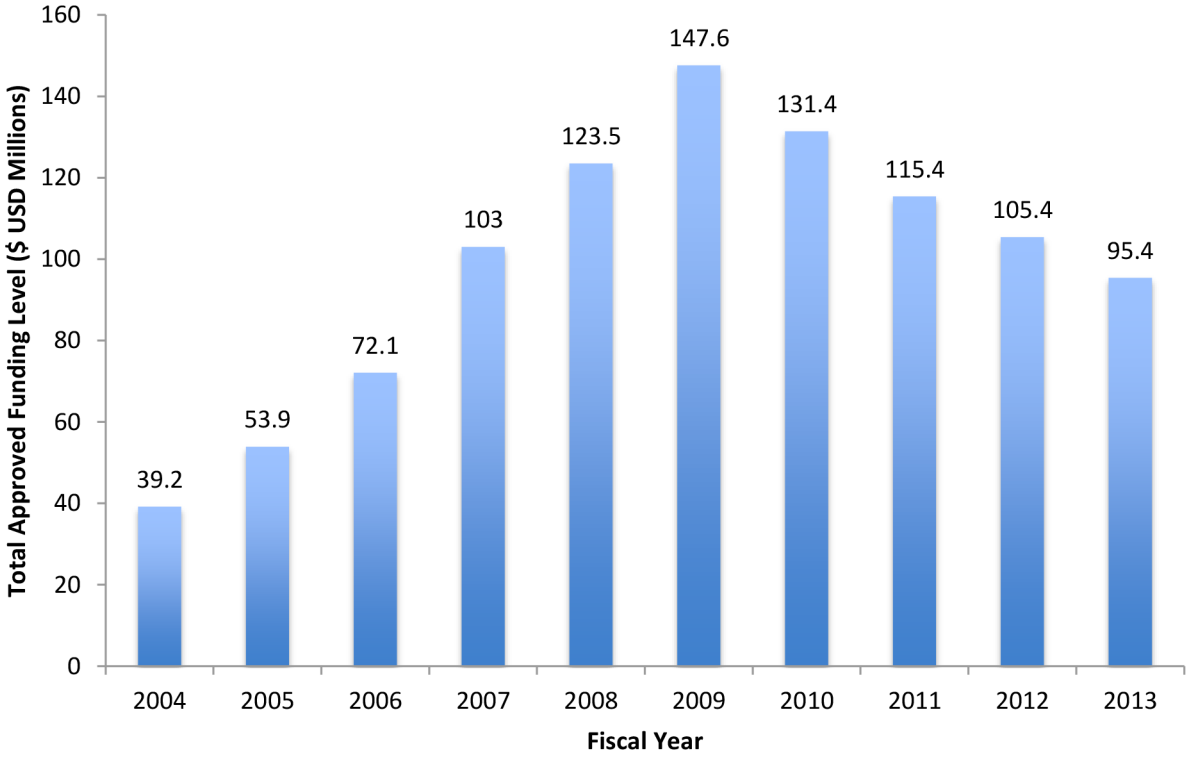

Fig 1. Total PEPFAR approved funding to Rwanda for HIV, tuberculosis (TB)/HIV, and health systems strengthening, 2004–2013. Sources: FY2004–2011: http://www.pepfar.gov/documents/organization/199598.pdf; 2012: http://www.pepfar.gov/documents/organization/212155.pdf; 2013: http://www.pepfar.gov/documents/organization/222179.pdf. FY, Fiscal Year.

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Table 1. Key HIV Program Indicators in Rwanda, 2005–2013.

HIV Program Indicator	2005	2006	2007	2008	2009	2010	2011	2012	2013
Number of individuals who received testing and counseling services for HIV and received their results	687,656	895,324	1,272,848	1,503,503	1,938,507	2,400,731	3,134,423	3,633,647	3,940,775
Percentage of adult population aged 15–49 years who reported having received an HIV test in the last 12 months	(DHS 2005) 11.6% women, 11.0% men					(DHS 2010) 38% women, 37.7% men			
Percentage of pregnant women living with HIV who received ART for PMTCT (%)	56	71	82	84	70[a]	68	79	90	92
Percentage of HIV-infected persons eligible for antiretroviral treatment who received it (%)	45.5	69.1	82.2	65.3[b]	75.8	83.3	89.3	91.5	92.0

Source: Data obtained from Tracnet and the 2005 and 2010 Rwanda Demographic and Health Surveys (DHSs). ART, antiretroviral therapy.

[a] Reduction from 2008–2009 due to guideline changes and phased implementation of option B, B+ for Prevention of Mother to Child HIV Transmission (PMTCT);

[b] Reduction from 2007–2008 due to increased number of people in need of ART (denominator) resulting from change of national immunologic eligibility criteria from less than 200 to less than 350 cells/mm^3 cluster of differentiation 4 (CD4) count.

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policies that permit for task shifting of services, helped to expeditiously provide universal and comprehensive HIV services throughout the country in a geographically equitable manner.

From the onset, GOR sought to expand its involvement in the direct management of its externally funded health and HIV programs given its commitment to national ownership as articulated in *Vision 2020* [8]. In 2009, Rwanda and its PEPFAR-funded partners aligned to support a second "sustainability and country ownership" phase of the AIDS response, which promoted the transition of HIV clinical service program leadership from partnering nongovernmental organizations (NGOs) to the host country [1,13]. Key within the transition plan developed by Rwanda and its partners was to allow for direct PEPFAR financing to the host country government. The plan also employed existing PEPFAR-funded international NGOs working in Rwanda and experts in HIV program management to accompany GOR as it learned how to best manage PEPFAR-supported programs. By February 2012, program transition occurred: Rwanda's Ministry of Health (MOH) became a direct recipient of PEPFAR funds and was responsible for coordinating comprehensive HIV services for nearly 40,000 patients in 76 health facilities.

Prerequisites for Transition: The Foundation for Sustainability

The following seven principles were instrumental in building a foundation that permitted for this successful HIV program leadership transition to occur.

Political Context of Decentralization

Rwanda's decentralization policy, implemented in 2005, empowers administrative districts, led by mayors, to coordinate all health activities undertaken within their district health facilities and health-oriented NGOs. Rwanda's network of 45,000 community health workers (CHWs) is the backbone of the country's health care system, providing care at the village level. This care then integrates with more advanced care provided at health centers in sectors, district hospitals, and referral hospitals at the central level. The decentralized nature of Rwanda's health system permitted for effective expansion of HIV services to health facilities in districts. For example, the number of health facilities providing Prevention of Mother to Child HIV Transmission (PMTCT) services increased nationwide from 53 in 2003 to 404 in 2011.

Ownership through National Coordination

From the beginning, Rwanda endorsed "the three ones" governance principle for its national AIDS response: one national HIV coordinating body, one national HIV strategic plan, and one national monitoring system [14]. NGOs operating in Rwanda with PEPFAR funding were committed to the long-term objectives in the national plan and aligned their HIV service delivery activities accordingly. Harmonizing HIV service delivery approaches across different NGOs early on expedited the eventual consolidation and transfer of these programs to MOH management.

Participation and Partnership

The national HIV prevention, treatment, and mitigation guidelines were developed through an inclusive, participatory process among key implementation stakeholders (national and international NGOs as well as the beneficiaries). As a result, partners employed the MOH comprehensive HIV treatment protocol, which promoted a common system of procurement and distribution of HIV drugs and consumables. Partners strengthened HIV leadership capacity at MOH through management training, direct skills transfer, and technical support to develop national tools and electronic systems to track HIV program activities at central, health facility, and community levels. This collaboration leveraged synergies across the health sector and accelerated universal access to HIV care and treatment. Further, the sense of solidarity, partnership, and trust between PEPFAR, the international NGOs, and MOH garnered through these experiences was critical for the eventual transition of HIV program leadership from partners to GOR in 2012.

Equity

Before these partnerships existed to support a more robust HIV response in Rwanda, Rwanda's MOH worked with civil society to develop an equitable approach for allocating limited antiretroviral therapy (ART) for people living with HIV (PLWH). Each health facility providing ART created an enrollment committee comprised of health professionals, social workers, and representatives of local associations of PLWH to ensure that the most vulnerable had access to treatment. Once there was sufficient treatment for all through PEPFAR funding, this committee was transformed into a therapeutic committee to improve support for PLWH retention in treatment. Moreover, from 2003 onwards, to assure equitable geographic access to treatment, GOR coordinated with its partnering NGOs to assume regional responsibilities. To ensure adequate staffing of these new HIV clinics that were being created to optimize geographic equity to care, a complementary program to build an appropriately trained workforce was developed. This assured the delivery of sophisticated HIV health services in remote areas, facilitating PLWH to be treated near their own communities by Rwandan health professionals under the authority of their own local governmental leaders.

Efficiency

Operationalizing the geographic mandate of NGO partners reduced implementation costs and promoted efficiency by discouraging duplication and improving coordination. In addition, the national plan required that each NGO partner undertake the full range of HIV services and support supervision, training, and mentorship in an integrated manner. This approach reduced the number of partners and logistics- and transport-related costs, all of which helped to streamline the transition process to host country ownership of the HIV delivery system. In addition, GOR implemented nationally approved salary structures for health personnel in all facilities.

By adhering to this salary policy, NGO partners helped to promote staff retention across facilities; this simplified the transition process as health personnel status and salaries remained unaffected once MOH assumed responsibilities for HIV program management in 2012.

Accountability

Rwanda has implemented a number of transparency, anticorruption, and quality assurance policies for all sectors, including health [15,16]. In 2003, the National AIDS Control Commission created a project management unit to oversee the donor funds for the HIV response directly managed by GOR. However, at the time, Rwandan health institutions had limited financial and administrative capacity to manage the program. Thus, to rapidly implement HIV programs funded by PEPFAR, the USG provided funding directly to international NGOs (rather than directly to GOR) to support the expansion of HIV-related services. Over time, these partnering NGOs helped build the administrative and programmatic capacity of Rwandan institutions at the central, district, health facility, and community levels, with an emphasis on accountability for results.

Rwanda's HIV program performance improved steadily over the first 5 years of PEPFAR funding (Table 1) [17]. The quality of Rwanda's HIV program and financial management systems improved over this period, and donor confidence in its administrative and reporting mechanisms was bolstered [16]. Moreover, in 2010, Rwanda began to publicly report semiannual budget execution of domestic and development partners' projects during the MOH Joint Health Sector Review. These efforts laid the groundwork for the establishment of larger direct cooperative agreements between CDC and Rwandan institutions, which was necessary for successfully transitioning HIV program management from NGO partners to GOR.

Integration of HIV Care to Strengthen the Health System

Since 2003, Rwandan and international stakeholders have embraced a shared vision that controlling the HIV epidemic requires integration of HIV services within the existing health system. The national policy was to create a sustainable system for Rwandans to manage HIV services for the long term without creating a parallel service delivery system. Partnering NGOs (such as the International Center for AIDS Care and Treatment Programs [ICAP] at Columbia University and AIDSRelief) supported Rwanda's national policy and applied the chronic disease model to HIV care as a way to strengthen critical components of the Rwandan health system such as infrastructure, personnel, supply chain, clinical management, information systems, and laboratory services [18]. This alignment with Rwanda's national policy improved integration of HIV patient services and yielded benefits across the entire health system with respect to HIV funds. This allowed Rwanda to build an integrated health service delivery platform, in which HIV could be addressed as a chronic disease.

Implementing Transition: Overcoming Challenges

Despite the gains made through the effective partnership during the early years of HIV program scale-up, there were several challenges Rwanda encountered when implementing the management transition of PEPFAR-funded HIV programs in 2009.

First, Rwanda's MOH initially lacked the human resources capacity and technical expertise needed to effectively manage the national scale-up of PEPFAR programs. Despite this limitation, MOH was eager to manage the PEPFAR-funded programs rapidly given the importance of national ownership of critical services delivered in Rwanda. However, during those early years of the emergency response to AIDS, the focus on expanding nationwide access to life-saving care and treatment prevailed over strengthening routine program management capacity.

Rwanda could have benefited from taking on more responsibilities for service delivery and reporting even earlier than the transition schedule permitted. This tension between respecting host country ownership and being pragmatic about implementation capacity limitations presented numerous challenges at the onset. Such challenges, however, were overcome through consistent, open communication between GOR and USG partners and the shared vision to optimize access and quality of HIV services provided to all Rwandans in need.

Second, once it became time for implementing NGOs to transition program management to GOR, partners faced an ambitious timeframe to complete this process. Specifically, the transition time mandated by USG meant that between 2009 and 2012, a total of 56,568 HIV-infected patients in care (including 25,206 patients on ART) needed to be transferred to different support systems in a seamless manner and without compromise of the quality of care. To meet this objective, a transition task force was formed, comprised of key Rwanda MOH officials, partner NGOs, and CDC, to both plan and monitor the transition of the 76 health facilities involved with HIV care delivery at the time. A key goal for the task force was to maintain the quality of HIV clinical services throughout the transition, using a jointly agreed timeline with clear performance indicators. The task force conducted readiness, baseline, and follow-up assessments and reviewed program data to identify gaps and areas for improvement. Through reconfiguring staff where needed, meeting regularly with stakeholders, routine visits to health facilities, and improved mentorship and supportive supervision from the central level, the program was transitioned to MOH with sustained clinical and management performance 24 months after transition. This task force illustrates the importance of partners committing to jointly monitoring program performance throughout a transition period. Resource-limited countries are likely to require extensive technical support from partners to reach this decision point. Development partners on the other hand need to be willing to reinforce their support for mentorship, quality improvement, and monitoring and evaluation.

Looking Ahead

Over the past 10 years, Rwanda has developed the expertise and experience to successfully manage a large cohort of HIV-infected individuals, and its clinicians are now able to provide high-quality care to patients at all stages of HIV disease. When PEPFAR partners like ICAP and AIDSRelief transitioned their responsibilities, some of their experienced staff were directly transferred to Rwanda's MOH to assist in the mentorship of the program managers and health care providers. However, as scientific knowledge advances and HIV prevention and care evolves, Rwanda may still need more advanced technical assistance to help address HIV transmission hot spots, HIV drug resistance, novel drug regimens, improved diagnostic testing methods, and long-term sequelae of HIV and its treatment. The Rwandan government has contracted with more than 20 American academic institutions with the aim to improve the quality of teaching of Rwandan health professionals, in order to be ready for the upcoming changes in the clinical management and quality improvement of the HIV response and to address other health threats [19]. In addition, as the resources for the global HIV response are plateauing and Rwanda's health sector is mandated to meet diverse health needs of its population, it is important to further prioritize the available resources towards higher-impact interventions in order to achieve greater results. The continued support of development partners is critical as the country finds its way to self-reliance while building a strong health system.

Conclusions

A decade ago, HIV was a mortal threat to the Rwandan people and an overwhelming challenge for the Rwandan health system. Today, Rwanda has a robust system for delivering quality care

to all those affected by HIV [20]. This was possible through the collaboration between GOR and its partners to develop a program from the onset that would allow for national ownership, sustainable development, and patient-centered health care [19].

Rwanda's HIV program transition experience illustrates both the importance of building capacity and systems within host countries to manage programs as well as the importance of jointly monitoring results to bolster collaboration. Several prerequisites that enabled the successful HIV program transition in Rwanda were identified, including understanding the political context of integration and decentralization, ownership through national coordination, participation and partnership, equity, efficiency, accountability, and developing HIV delivery systems that simultaneously strengthened the entire health system.

Transition of donor-funded programs to country management is an important step on the development pathway and should be built into any program at the very beginning for more efficiency. To offer life-saving services to their people in a sustainable way, governments should strategize with their partners to achieve program transition of HIV delivery and beyond. Countries should seek more program management responsibility and request—as needed—specialized external technical support that helps to assure access to care, high quality, and accountability for the populations in need.

Author Contributions

Contributed to the writing of the manuscript: AB IK EK JPN SN FM RKK VM RS CB LI AA WMES PLR KWS. Wrote the first draft of the manuscript: AB IK EK PLR. Agree with the manuscript's results and conclusions: AB IK EK JPN SN FM RKK VM RS CB LI AA WMES PLR KWS. All authors have read, and confirm that they meet, ICMJE criteria for authorship.

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Building Global Epidemiology and Response Capacity with Field Epidemiology Training Programs

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More than ever, competent field epidemiologists are needed worldwide. As known, new, and resurgent communicable diseases increase their global impact, the International Health Regulations and the Global Health Security Agenda call for sufficient field epidemiologic capacity in every country to rapidly detect, respond to, and contain public health emergencies, thereby ensuring global health security. To build this capacity, for >35 years the US Centers for Disease Control and Prevention has worked with countries around the globe to develop Field Epidemiology Training Programs (FETPs). FETP trainees conduct surveillance activities and outbreak investigations in service to ministry of health programs to prevent and control infectious diseases of global health importance such as polio, cholera, tuberculosis, HIV/AIDS, malaria, and emerging zoonotic infectious diseases. FETP graduates often rise to positions of leadership to direct such programs. By training competent epidemiologists to manage public health events locally and support public health systems nationally, health security is enhanced globally.

In 1951, in response to the threat of biological warfare during the Korean War, the Communicable Disease Center (now the US Centers for Disease Control and Prevention; CDC) established the Epidemic Intelligence Service (EIS) to respond to infectious disease outbreaks (*1*). The 2-year training program used a learning-while-doing approach to develop field epidemiologists (or disease detectives) capable of rapidly investigating and curtailing public health threats. The EIS has served as the model for developing a similar program, called the Field Epidemiology Training Program (FETP), around the world (*2*).

In 1975, the first FETP outside the United States was established in Canada. In 1980, Thailand launched the first FETP outside of North America, with CDC support (*3*). Since then, FETPs have been established in ≈65 countries around the world, many with assistance from CDC, the World Health Organization (WHO), the European Centre for Disease Prevention and Control, and other public health organizations. In many countries, FETPs have proven to be successful models for building public health workforce capacity (*4*); however, critical gaps remain in epidemiologic capacity including, for example, the 3 countries in West Africa where the 2014–2015 Ebola epidemic arose and propagated widely (*5*).

In 2003, the outbreak of severe acute respiratory syndrome (*6*) highlighted the continued worldwide vulnerability to infectious disease threats brought by ever-expanding global travel and trade. In response to severe acute respiratory syndrome and similar threats, WHO revised the International Health Regulations in 2005 (IHR 2005) to define core capacities necessary for countries to detect and respond to public health threats (*7*). Unfortunately, many countries remain unprepared to meet IHR 2005 requirements. In 2014, the Global Health Security Agenda (GHSA) was launched by the United States with 28 partnering nations, WHO, the Food and Agriculture Organization, and the World Organisation for Animal Health. The GHSA purpose was to accelerate progress toward implementation of IHR 2005 so that all countries are able to rapidly detect, respond to, and control public health emergencies at their source and thereby ensure global health security (*6*). One of these core elements is adequate human resources, which is essential for achieving each of the other IHR 2005 capacities. Highlighting the role of workforce development in accelerated IHR 2005 implementation, WHO revised the IHR 2005 monitoring framework and the Joint External Evaluation tool (which is used to measure progress toward IHR 2005 and GHSA implementation) to include specific public health workforce targets that rely on having an "applied epidemiology training program in place such as FETP" (*8*). By 2014, however, nearly 70% of countries had still not achieved IHR 2005 compliance, and few countries had achieved the Joint External Evaluation target of having 1 trained field epidemiologist (or equivalent) per 200,000 population.

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We describe the traditional 2-year FETP that has been supported by CDC in many countries. We also describe the effect of FETPs; their role in the development of a public health workforce; and how FETPs are enhancing the capacity of countries to rapidly detect, respond to, and control public health threats and thereby enhance global health security.

Building Field Epidemiology Capacity Globally

CDC supports FETP development to strengthen countries' epidemiology, surveillance, and response capacity, thereby enhancing global health security through a well-trained public health workforce. CDC support has included placement of a resident advisor in the country, technical support, and financial support. The resident advisor is an experienced applied epidemiologist, usually a graduate of the CDC EIS program or another FETP, who is placed in the country during the first few years of a new FETP to guide training and provide technical assistance. Since 1980, CDC has supported the launch of ≈45 FETPs with participants from ≈64 countries; numbers have increased since 2000 (Figure 1). Almost all of these FETPs continue to recruit and train epidemiologists, and many function independently of CDC funding. As of December 2016, there were 65 FETPs in 90 countries, and CDC was supporting 30 FETPs-Advanced serving 49 countries (Figure 2); ≈3,900 field epidemiologists have graduated from these CDC-supported programs.

FETPs traditionally have been 2-year programs that are based in ministries of health and that provide advanced field epidemiology training and service; however, shorter FETP models now exist. Participants (residents) in the FETPs-Advanced, usually ministry of health physicians and other professional staff, learn and practice epidemiologic skills while delivering essential epidemiologic services (training through service) to the ministry at the national or subnational level. FETP residents contribute to ministry missions by reviewing and analyzing surveillance data, detecting and responding to disease outbreaks and other public health emergencies, and conducting planned studies of public health priorities. They also develop skills to conduct public health research, improve communication of scientific findings, translate those findings into public health action, and contribute to the network of field epidemiologists locally and worldwide (*9*,*10*).

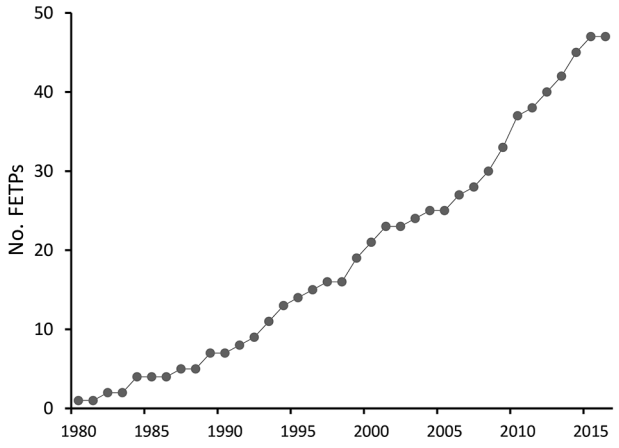

Figure 1. No. Field Epidemiology Training Programs (FETPs) established with US Centers for Disease Control and Prevention engagement (previous and current), 1980–2016.

As a fundamental feature, FETPs use the learning-by-doing approach with mentored public health practice for ≥70% of program time (*4*,*11*). However, programs are tailored to suit the needs and conditions of individual countries and regions. For example, although the focus for most programs is national, for a few programs it is regional (e.g., Central America, French-speaking West Africa, central Asia) (*12*,*13*), and some national programs accept residents from smaller neighboring countries. Many FETPs partner with a university to provide a postgraduate degree to residents who successfully complete the field and academic requirements, and some offer medical board qualification in community medicine or epidemiology. Some programs have included a laboratory track (Field Epidemiology and Laboratory Training Program; FELTP) (*14*), a veterinary track, or both, and 1 has a parallel veterinary FETP for animal health. The Central America program addressed the need for improved surveillance and epidemiology practice at all levels of the public health system by developing a 3-tiered FETP training model (Basic/Frontline, Intermediate, and Advanced) to build capacity at each level (*12*,*15*). Each tier aims to improve competency of public health workers in the same 4 essential domains of field epidemiology—surveillance, field investigation and response, data collection and analysis, and scientific communication—but the expectations are tailored to the public health skills needed at that level. FETP-Frontline training for surveillance officers has been implemented throughout Africa, Latin America, and elsewhere in response to the Ebola epidemic in West Africa, the Zika virus threat in the Americas, and the adoption of the GHSA (a global initiative to strengthen capacity to prevent, detect, and respond to public health threats). As of the end of 2016, a total of 24 new Frontline programs had been established and 1,354 surveillance staff had been trained (*16*).

During the 1990s, directors of several FETPs and similar programs organized themselves into a global network to expand program reach and to ensure program quality. In 1997, the network was formalized as the Training Programs in Epidemiology and Public Health Interventions Network (TEPHINET) (*17*). TEPHINET now has 69 member programs in its global network. Over the years, as the number of FETPs has expanded, regional networks have been developed to support program implementation and strengthening. The African Field Epidemiology Network formed in 2005 (*18*), the Eastern Mediterranean Public

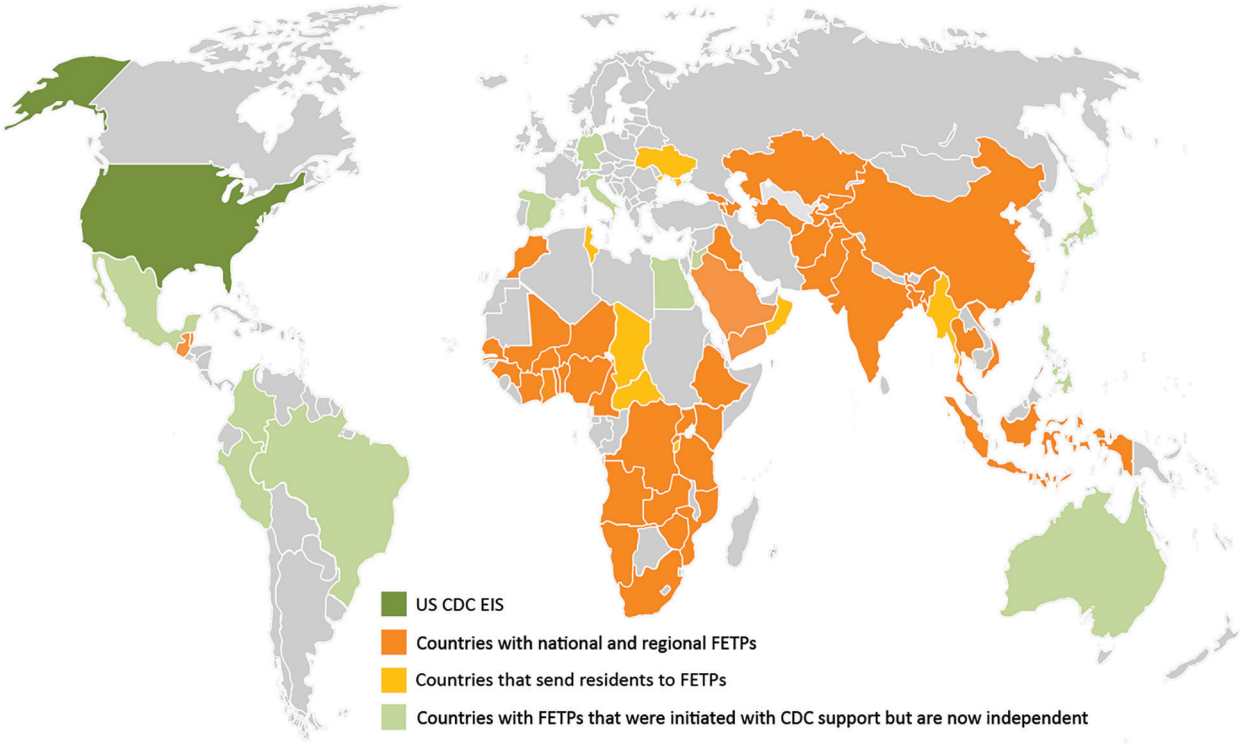

Figure 2. FETPs-Advanced presently or previously associated with CDC, as of December 2016. India supports 2 FETPs-Advanced; both were initiated with CDC support, and 1 is now independent. Central America has had an FETP-Advanced that was paused in 2015 and restarted in August 2017 with Guatemala and Belize. CDC, US Centers for Disease Control and Prevention; EIS, Epidemic Intelligence Service; FETP, Field Epidemiology Training Program.

Health Network (*19*) and the South East Asia Field Epidemiology and Technology Network in 2009, and the South American Field Epidemiology Training Programs Network and the Association of Southeast Asian Nations Plus Three Field Epidemiology Training Networks in 2011.

TEPHINET, along with its member programs and CDC, has recently developed and implemented an accreditation process for FETPs-Advanced (http//:www.tephinet.org/accreditation). Accreditation was initiated in response to the increasing numbers of programs and the variations in their implementation. Its goal is to maintain and improve program quality (*20*,*21*). The process has received wide support from FETP program directors (D. Herrera, TEPHINET, pers. comm., 2017 Feb 28). The first 3 programs (EIS, Canadian Field Epidemiology Program, and the UK FETP) were accredited in 2016, and more programs have applied for accreditation in 2017.

Outcomes and Effects of FETPs

The goal of FETPs is to develop competent field epidemiologists who can assume priority public health positions while strengthening countries' outbreak response capacity, surveillance systems, and use of data to inform prevention and control measures for priority public health problems. The following examples demonstrate the value of a strong public health workforce and improved surveillance, outbreak response, and data use capacity for greatly enhancing national, regional, and global health security.

Outbreak Investigations and Emergency Responses

Since 2005, FETP residents have responded to ≈3,300 outbreaks (Figure 3). Although many of these outbreaks were local, the experience prepared FETP residents to handle problems of national and international concern.

During the recent Ebola epidemic in West Africa, ≈70 FETP residents and graduates from ≥9 African nations and Haiti participated in investigation and response activities. They served as epidemiologists, surveillance officers, contact tracing supervisors, and laboratorians in support of epidemic control (*22*) (L. Boulanger, CDC Ethiopia, pers. comm., 2017 Mar 23). In 2015, the residents and graduates of the Nigeria FELTP supported a contact tracing effort that prevented a major Ebola epidemic in that country, in contrast to the unchecked spread in neighboring countries without FETPs (*23*,*24*).

In February 2015, the 10 residents of the Uganda FETP were called to investigate an outbreak of a strange

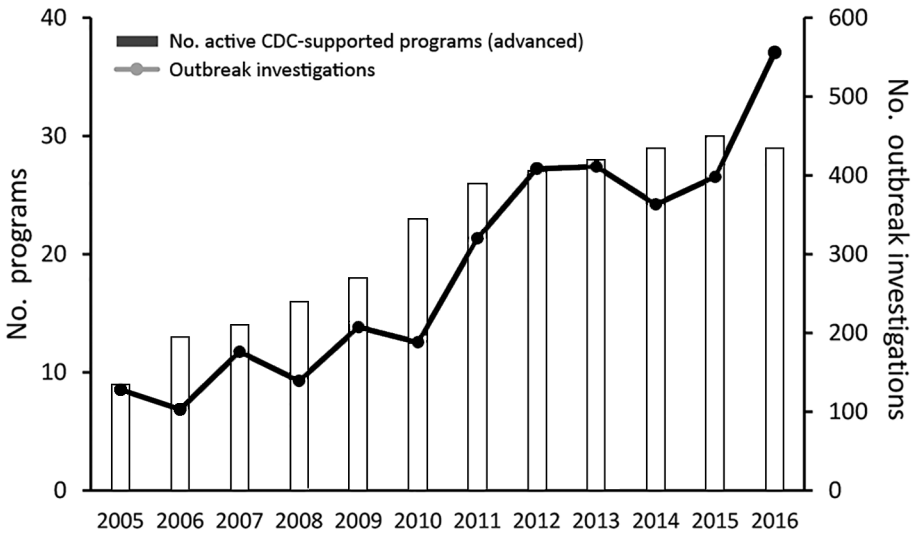

Figure 3. Outbreak investigations conducted by residents (participants) in US Centers for Disease Control and Prevention (CDC)–supported Field Epidemiology Training Programs, 2005–2016.

disease that had killed 1 person and sickened 24 more in Kampala, the capital of Uganda. Investigation by the residents uncovered a much more widespread outbreak of typhoid fever that had spread insidiously throughout Kampala. They identified the cause as contaminated water from uncontrolled underground sources (*25*). Guided by this epidemiologic investigation, international institutes and organizations from Uganda and elsewhere mounted a major coordinated response and contained the outbreak.

In May and June 2013, the India Epidemic Intelligence Service (India EIS), an FETP in India, investigated an outbreak of unexplained encephalopathy in which 133 children were hospitalized and 59 (44%) died. Similar outbreaks had been noticed since 1995, but multiple attempts to find a cause and control the disease had failed. The India EIS noted that many of the affected children were hypoglycemic, a characteristic of patients with ackee fruit encephalopathy. They also noted that litchi (also called lychee) fruit, a relative of the ackee, was commercially cultivated in the area. When the outbreak recurred in 2014, the India EIS demonstrated a strong epidemiologic association between encephalopathy and litchi consumption; laboratory testing confirmed the presence of the toxins methylenecyclopropylglycine and hypoglycin A in affected children and in litchi. Evidence-based recommendations were developed to prevent future seasonal outbreaks and associated deaths (*26*).

In 2007 in China, paraplegia suddenly developed in leukemia and lymphoma patients while they were receiving weekly intrathecal injections of drug. Without an identified cause, the intrathecal drugs were embargoed, thus limiting treatment availability. Investigation by epidemiologists and residents of the China FETP led to the identification of contamination with minute quantities of vincristine, a potent neurotoxin (*27*). These findings enabled correction of the problem and resumption of intrathecal drug production and use.

Surveillance System Support

During their training, all FETP residents are expected to analyze, use, and improve surveillance data. Surveillance systems addressed by FETP residents include those for routinely reported notifiable diseases; specific diseases, such as HIV infection; and noncommunicable conditions such as maternal death, injury, and birth defects (*28*,*29*).

During the 2014 outbreak of Middle East respiratory syndrome (MERS) in Jeddah, Saudi Arabia, several graduates from the Saudi Arabia FETP were asked to strengthen the surveillance system for MERS. The graduates tackled numerous issues such as nonuse of the case definition for selection of laboratory testing, delayed laboratory reporting, and inconsistent case counts among sources. The FETP team redesigned the system to enable simultaneous real-time electronic reporting of suspected and confirmed cases to public health professionals who needed to take essential control and preventive actions on new cases. The system, now run by another FETP graduate, provides real-time data on MERS in Saudi Arabia and is used to populate the widely distributed, weekly Saudi MERS report that is redistributed by WHO (A. Alzahrani, King Faisal Specialist Hospital and Research Center, pers. comm., 2017 Feb 7).

FETPs also develop and support surveillance and response systems during mass gatherings for sporting, religious, and other events. During the Fédération Internationale de Football Association World Cup held in South Africa in 2010, FETP residents helped establish and run surveillance and response systems to protect the public health during these events. The 22 FETP residents supported the collation and analysis of data from

the 9 provinces and participated in investigation of ≈20 suspect public health events (*30*) (L. Kuonza, South Africa FETP, pers. comm., 2017 Feb 2). Similarly, during religious mass gathering events in Saudi Arabia, Pakistan, Morocco, Iraq, and Jordan, FETP residents in those countries supported surveillance and other public health activities (*31*–*34*).

FETP-trained personnel also participate in surveillance activities during national disasters. In 2010, when floods covered 20% of Pakistan, FETP-trained officials were mobilized to help their provincial departments of health. They developed and maintained surveillance and responded to outbreaks in the camps of displaced populations. This workforce provided vital public health services, including planning; coordination; data collection, analysis, and interpretation; emergency preparedness and response; and outbreak investigations in multiple districts (*35*).

FETPs have also strengthened laboratory surveillance. The South Caucasus FELTP expanded the existing anthrax surveillance to include poxviruses, leading to improved diagnosis and control for anthrax and identification of a novel poxvirus (*36*).

Control and Prevention of Priority Public Health Problems

FETPs play critical roles in addressing priority public health problems in countries, often with the collaboration and support of international initiatives such as the US President's Emergency Plan for AIDS Relief (*37*,*38*), the President's Malaria Initiative (*39*,*40*), and the Global Polio Eradication Initiative (*41*,*42*). This approach ensures that residents' work supports national and global priorities while the residents practice applying epidemiologic methods to these programs and providing public health service.

As an example, FETP residents have broadly supported polio elimination in Nigeria and Pakistan through National Stop Transmission of Polio (N-STOP) programs. FETP Pakistan designed the first N-STOP program to meet the need for local public health staff to fight polio in that country. The North Waziristan area, a highly security-compromised area, reported 20% of all global cases of polio in 2014. Despite ongoing military operations and human displacement, FETP Pakistan placed 2 residents as N-STOP officers in the North Waziristan area and the adjoining South Waziristan area. The residents, working under difficult and hazardous conditions, rebuilt the infrastructure for surveillance and polio eradication activities and persuaded other staff to return. The transmission of polio virus was interrupted in the North Waziristan area (cases decreased from 70 in 2014 to 0 in 2016) and substantially reduced in the South Waziristan area (cases decreased from 24 in 2014 to 2 in 2016) (*42*).

In Nigeria, the N-STOP program has developed innovative strategies to address polio eradication challenges. One N-STOP initiative focused on locating and vaccinating children <5 years of age in remote, nomadic, scattered, and border populations in northern Nigeria where low polio vaccination coverage probably contributed to ongoing transmission of wild polio virus. During August 2012–April 2013, N-STOP conducted field outreach activities that enumerated ≈40,000 remote settlements, including 4,613 settlements never visited by vaccination teams during previous polio supplemental immunization activities (*41*,*43*).

Graduates

Training competent field epidemiologists for a country builds long-term capacity only if the country uses FETP graduates in appropriate positions of public health responsibility. Some countries have developed specific positions for graduates, such as provincial epidemiologist. Other countries have modified the requirements for certain positions to include FETP certification. Overall, most FETP graduates are retained within their country's public health systems, and many rise to positions of public health responsibility. We estimate that ≈80% of recent graduates continue to work for the national ministry of health or equivalent. In many countries, this figure approaches 100%. Graduates have served as permanent secretaries for health; ministers of health; and program directors for epidemiology, surveillance, and specific disease control programs. Others have held responsible positions with WHO (e.g., national professional officers) and nongovernmental public health–associated organizations.

A valued role for graduates is leadership within the FETP itself. The national FETP director and other technical staff are usually FETP graduates. Graduates serving in national and other public health positions are specifically groomed to serve as mentors for the residents during their field placements. Experienced graduates have also been hired to serve as resident advisors of newly developed FETPs in other countries.

Building Institutionalized and Sustainable FETPs

Most FETPs were initiated with financial and technical support from external donors and partners (*3*,*4*). The costs for developing programs vary widely and, among other considerations, depend on the size, model, and partners involved (*10*). To ensure their continuity and long-term contribution toward strengthening public health, the programs are anchored within the ministries of health or other public health institutions. This national ownership ensures that the FETPs contribute to tangible and relevant delivery of essential epidemiologic services from the outset.

Recognizing FETPs as valuable for addressing national health priorities has helped to institutionalize and sustain FETPs (*11*,*44*). Many programs have been operating independently for years and have become national resources for disease surveillance, public health emergency response, and priority public health disease prevention and control programs (*45*,*46*).

Of the 19 programs that were established during 1980–2000 with CDC engagement, 17 continue to produce graduates and provide service. The principal elements for program institutionalization and sustainability include establishment of an organizational structure and institutional ownership within the ministry of health or other public health institution, national leadership from FETP graduates, focus on priority- and science-based training, communication of findings and recommendations to the public health leadership, assurance of a recognized career path for graduates, and continued engagement between graduates and the FETP (*20*). CDC works with programs to support these elements and to help ensure their long-term success.

Challenges

Despite progress in building sustainable institutionalized programs, several challenges remain. New FETPs commonly struggle to identify sufficient numbers of qualified epidemiologists to serve as mentors until graduates can become mentors at least 2 years later. Ministries of health commonly wrestle with the challenge to develop and maintain appropriate career paths for FETP graduates. In the absence of appropriate available positions, graduates often resume their pretraining roles, which probably underutilize their new epidemiologic skills. Committed ministries of health have had varying levels of success in addressing this problem, depending on the structure and limitations of their human resources systems (*47*,*48*). A final challenge is that uncertain political support within the health system, funding limitations in the face of competing priorities, and weaknesses in the healthcare infrastructure can threaten support for FETPs and prevent establishment of a sufficient institutional framework to ensure long-term survival. CDC works with programs to identify and engage numerous disease initiatives and multisectoral global health activities to develop new partnerships to support programs as they develop (*49*). To highlight the contribution of FETPs and promote their sustainability in countries around the world, continuous advocacy is essential.

Conclusions

In this age of globalization and the emergence of new and resurgent communicable diseases (e.g., Ebola, Zika, MERS) and the increasing global effects of known diseases (e.g., yellow fever, dengue fever), qualified field epidemiologists are needed more than ever. There is a critical need for good epidemiologic science in all countries to support prevention and control programs for communicable and noncommunicable diseases, injuries, and environmental hazards. The adoption of the IHR 2005 standards and the development of the GHSA have made clear that every country needs at least a minimum capacity in field epidemiology to rapidly detect, respond to, and control public health emergencies and thereby keep its population safe, protect other countries from the spread of illness, and ensure global health security. The development of FETPs across the globe is recognized as being critical for meeting that need and therefore for enhancing global health security (*50*). It will be crucial to maintain and continue to improve the quality and reach of FETPs in countries through expanding the number of countries with access to these programs and expanding the tiered training within countries. The global public health community, working together with international partners and the global network of FETPs, can be instrumental in building on the strengths of the existing programs to broaden the beneficial effects of these critical capacity-building efforts.

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Viral Suppression in a Nationwide Sample of HIV-Infected Children on Antiretroviral Therapy in Rwanda

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Abstract: Rwanda has made significant progress in expanding pediatric antiretroviral treatment coverage. This was a nationwide, cross-sectional study of pediatric HIV suppression rates. Of 292 children on antiretroviral treatment ≥12 months, 68.8% achieved viral suppression < 40 copies/ml, respectively. Rwanda achieved good pediatric viral suppression rates, comparable to those from other resource-limited settings, yet more efforts are needed to achieve the UNAIDS 90-90-90 target.

Key Words: Rwanda, HIV, pediatric, viral load, suppression

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Rwanda has achieved near universal treatment coverage for adults in need of antiretroviral therapy (ART). However, despite this accomplishment, and similar to global trends, pediatric treatment coverage lags far behind, with only 53% of Rwandan children actually receiving ART.[1] The treatment program has scaled from 24 sites providing pediatric ART in 2004 to 553 sites in 2016.

Virologic suppression rates in pediatric populations have ranged from 20–90% among sites in sub-Saharan Africa, Asia, the Caribbean, the United States and Europe.[2] In Rwanda, an early study of pediatric outcomes at 2 heavily supported health centers in Kigali found an 83% suppression rate among 144 children on ART after a median treatment duration of 18 months.[3] A subsequent prospective cohort of 123 children found 76% were virologically suppressed.[4] One concern about such studies, however, is that they may not be representative of all sites in a country where levels of support and provider experience may differ.

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Here, we present a cross-sectional study of virologic suppression rates among a nationally representative sample of HIV-infected children receiving ART in Rwanda.

METHODS

Study Design, Population and Setting

This nationwide study was conducted from August to October 2011 in 45 randomly selected sites across all 5 provinces of Rwanda. HIV-infected children 0–14 years of age at the time of ART initiation, who started ART on or after January 1, 2007, and returned for routine clinical follow-up testing at 1 of the selected sites were included.

Study Procedures

Patient charts and site registers were reviewed to identify all eligible children at the selected sites. Three hundred ten (92.8%) of 334 eligible children returned for VL testing. Blood samples were drawn into specialized plasma preparation tubes by trained, site-based laboratory technicians. VL specimens were processed at the National Reference Laboratory (Kigali) using real-time quantitative polymerase chain reaction method COBAS Taqman analyzer CTM96.

Sampling of Sites

Of the 269 health facilities initiating children on ART at the time of the study, 129 sites were treating ≥ 15 pediatric patients. The number of 45 sites was determined by the Neyman allocation equation based on the estimated total sample size. Of these, 45 sites from all 5 provinces in Rwanda were selected using a stratified random sampling method based on probability proportional to size allocation; of the 3 size-based categories, the sites included were chosen in the following proportions: 35 small facilities (treating < 45 children), 7 medium facilities (45–90 children) and 3 large facilities (> 90 children).

Sampling of Study Population

Where available, ART registers were used as patient sample frames. If the registers were not available, numbers were assigned to patient cards and a pre-prepared random listing of numbers corresponding with patient records at the facility were used to randomly select the required number of charts. The number of children to be selected per facility was determined based on the size of the site: 12 children in small facilities, 48 children in medium facilities and 91 children in large facilities. Within the facility, simple random sampling was used to select patient records.

Measurements

Outcome Variable

The primary outcome of interest for this study was virologic suppression. Virologic suppression was evaluated using 2 definitions: VL < 400 copies/mL, as recommended by the Centers for Disease Control and Prevention for settings relying on dried blood spot for testing, and VL < 40 copies/mL, based on current Rwanda National HIV Guidelines.

Explanatory Variables

The demographic, clinical and immunologic covariates include sex, age at VL specimen collection, age at ART initiation, ART regimen at initiation, World Health Organization (WHO) clinical staging at presentation, length of time on treatment, immunodeficiency at ART initiation, nutrition status, type of facility (health center or hospital), treatment setting (rural or urban), hemoglobin, TB screening and status and co-trimoxazole prophylaxis.

Statistical Analysis

Data were analyzed using STATA (version 12) (STATA Corporation, College Station, TX). Descriptive statistics were used to characterize the demographic, clinical and immunologic variables for each defined age group. The odds ratios of VL suppression were estimated using bivariate analysis to identify potential risk factors and included in a multivariable analysis using a backward elimination method factors that were associated with VL in the bivariate analysis at ≤ 0.1 significance level to develop a final multivariate model. Variables with ≤ 0.05 significant level were retained in the final multivariate model.

RESULTS

Patient Characteristics

Of the 310 children enrolled in the study, the median age of the 292 (94%) who initiated ART and were retained throughout the study was 72 months (Table 1). Most (175, 59.9%) had been on ART > 24 months, and approximately half of the children visited health facilities in a rural area (50.3%). Only 14 children (5.3%) were on a protease inhibitors–based regimen. The remainder were receiving a regimen containing efavirenz or nevirapine in combination with lamivudine and either thymidine analogs (Stavudine or Zidovudine) or abacavir.

Viral Load Suppression

Of the 292 children initiated on ART, 68.8% were virologically suppressed at the end of the study (VL < 400 copies/ml; Fig. 1). After 12 months on ART, 66.7% (95% confidence interval [CI], 42.5–90.8%) and 77.8% (95% CI, 56.5–99.1%) of children achieved VL < 40 copies/mL and VL < 400 copies/mL, respectively. After 24 months of therapy, 54.3% (95% CI, 46.5–62.1%) achieved VL < 40 copies/mL and 66.1%(95% CI, 58.7–73.4%) VL < 400 copies/mL.

Predictors of Viral Suppression

At the level of bivariate analysis, none of the predictors (age at treatment initiation, sex, level of immunosuppression and ART regimen) was significantly associated with VL < 400 copies/mL (Table, Supplemental Digital Content 1, http://links.lww.com/INF/D188).

Ethics

Approval for the study was obtained from Rwanda National Ethics Committee as well as from Centers for Disease Control and

TABLE 1. Characteristics of 292 Children with HIV in Rwanda at Initiation of ART

Variables	All Ages N = 292	< 12 mo n = 19	12–35 mo n = 53	> 35–60 mo n = 49	> 60–120 mo n = 108	> 120 mo n = 63
Median age (mo)	72	7	24	47	88	137
Median hemoglobin (g/dl)*	12	11.6	10.8	11.6	12	12.6
Location of health facility (%)						
Rural	147 (50.3)	10 (52.6)	29 (54.7)	27 (55.1)	52 (48.2)	29 (46)
Urban	145 (49.7)	9 (47.4)	24 (45.3)	22 (44.9)	56 (51.9)	34 (54)
Type of health facility (%)						
Health center	177 (60.6)	13 (68.4)	30 (56.6)	27 (55.1)	69 (63.9)	38 (60.3)
Hospital	115 (39.4)	6 (31.6)	23 (43.4)	22 (44.9)	39 (36.1)	25 (39.7)
Sex (%)						
Male	142 (48.6)	10 (52.6)	28 (52.8)	25 (51)	53 (49.1)	26 (41.3)
Female	150 (51.3)	9 (47.4)	25 (47.2)	24 (49)	55 (50.9)	37 (58.7)
WHO stage at initiation (%)						
WHO 1 and 2	129 (44.3)	14 (73.7)	19 (35.9)	19 (38.8)	45 (41.7)	32 (51.6)
WHO 3 and 4	162 (55.7)	5 (26.3)	34 (64.2)	30 (61.2)	63 (58.3)	30 (48.4)
ART regimen (%)						
AZT + 3TC + NVP/EFV based	178 (67.7)	5 (26.3)	32 (65.3)	38 (86.4)	74 (77.1)	29 (52.7)
ABC + 3TC + NVP/EFV-based	71 (27)	5 (26.3)	13 (26.5)	6 (13.6)	21 (21.9)	26 (47.3)
PI-based	14 (5.3)	9 (47.4)	4 (8.2)	0 (0)	1 (1)	0 (0)
Immunosuppression (%)						
Not immunosuppressed	106 (37.6)	9 (60)	17 (36.2)	16 (32.7)	47 (43.5)	17 (27)
Immunosuppressed	176 (62.4)	6 (40)	30 (63.8)	33 (67.4)	61 (56.5)	46 (73)
Nutrition at initiation (%)						
Severe malnutrition	49 (20.7)	3 (16.7)	15 (28.3)	14 (30.4)	13 (12)	4 (33.3)
Moderate malnutrition	49 (20.7)	3 (16.7)	12 (22.6)	8 (17.4)	23 (21.3)	3 (25)
Mild/no malnutrition	139 (58.7)	12 (66.7)	26 (49.1)	24 (52.2)	72 (66.7)	5 (41.7)
Length of time on ART (%)						
< 24 mo	117 (40.1)	15 (78.9)	23 (43.4)	13 (26.5)	38 (35.2)	28 (44.4)
> 24 mo	175 (59.9)	4 (21.1)	30 (56.6)	36 (73.5)	70 (64.8)	35 (55.6)
TB status (%)						
No active TB	221 (80.4)	14 (82.4)	43 (86)	34 (70.8)	85 (82.5)	45 (78.9)
Active TB	54 (19.6)	3 (17.7)	7 (14)	14 (29.2)	18 (17.5)	12 (21.1)
Cotrimoxazole prophylaxis (%)						
No	7 (2.5)	0 (0)	1 (1.9)	2 (4.1)	4 (3.9)	0 (0)
Yes	279 (97.6)	19 (100)	52 (98.1)	47 (95.9)	100 (96.2)	61 (100)

AZT indicates Zidovudine; EFV, effavirenz; NVP, nevirapine; PI, protease inhibitors; TB, tuberculosis; 3TC, lamivudine.
Characteristics of the children presented according to age groups.

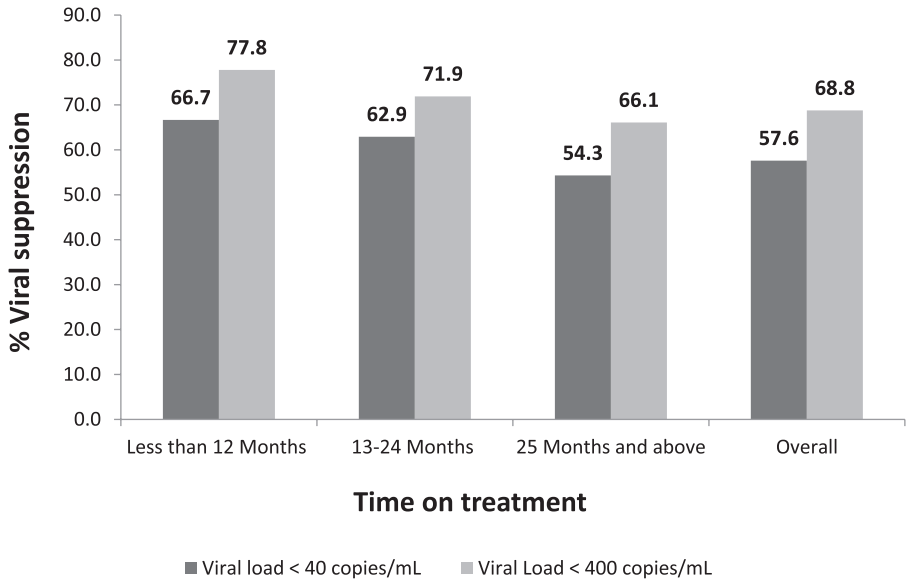

FIGURE 1. The proportion of children who attained viral load suppression less than 40 copies/mL and 400 copies/mL are depicted in blue and orange colors, respectively.

Prevention-Atlanta. Parents/caregivers of eligible children were asked to consent for their child's participation in the study. To avoid collecting the patient identifiable information that is standard on lab requisition forms, a unique study ID was developed and used to allow linkage of laboratory data to clinical information.

DISCUSSION

This study demonstrates that Rwandan children in the national ART program were able to achieve levels of viral load suppression similar to children in other studies conducted in Brazil, United States and some resource-limited settings. The virologic suppression rate in this study was comparable with other sub-Saharan country program evaluations.[4–6] There were no particular factors that significantly predicted virologic suppression despite differences in children's age, WHO stage at initiation, geographical location and type of health facility visited. Although overall viral suppression rates in these children need to improve, there does appear to be uniformity of outcomes within the structure of the Rwandan National Program.

The limited number of pediatric ART regimens, poor palatability, side effects, acquired primary resistance and the complicated nature of the available pediatric formulations make pediatric HIV management challenging. Pediatric ART is additionally complicated by changing weight-based dosing over time as children grow, and providers may not be routinely updating dosages over time, leading to inadequate drug concentrations and higher rates of virologic failure.

The strengths of this study are its national representation of children initiating ART in Rwanda, and these programmatic results are important for informing the national HIV program. The main limitations of this study are the relatively small sample size, the skewed age distribution and the limited number of variables evaluated as predictors. Additionally, stratification of the analysis by age may have been affected by the overrepresentation of children > 60 months of age. Because there was a small proportion of the sample in the < 12-month age group, the analysis may not be able to identify factors that affect children in this critical age group in particular. As the questionnaire used for data collection was limited primarily to clinical, immunologic and virologic variables this analysis may have missed other potential predictors of suppression such as adherence, psychosocial support, travel time to clinics and nurse versus doctor involvement that other studies have identified as being significantly associated with treatment outcomes.[4–8]

Rwanda has had rapid and tremendous success in controlling the HIV epidemic over the past decade.[9,10] These results demonstrate the feasibility of positive treatment outcomes measured by VL suppression in a pediatric resource-limited settings population; however, there remains work to be done to improve pediatric ART outcomes in Rwanda to achieve the 90-90-90 UNAIDS goals by 2020.

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Association of *Plasmodium falciparum kelch13* R561H genotypes with delayed parasite clearance in Rwanda: an open-label, single-arm, multicentre, therapeutic efficacy study

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For the French translation of the abstract see Online for appendix 1

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Summary

Background Partial artemisinin resistance is suspected if delayed parasite clearance (ie, persistence of parasitaemia on day 3 after treatment initiation) is observed. Validated markers of artemisinin partial resistance in southeast Asia, *Plasmodium falciparum kelch13* (*Pfkelch13*) R561H and P574L, have been reported in Rwanda but no association with parasite clearance has been observed. We aimed to establish the efficacy of artemether–lumefantrine and genetic characterisation of *Pfkelch13* alleles and their association with treatment outcomes.

Methods This open-label, single-arm, multicentre, therapeutic efficacy study was done in 2018 in three Rwandan sites: Masaka, Rukara, and Bugarama. Children aged 6–59 months with *P falciparum* monoinfection and fever were eligible and treated with a 3-day course of artemether–lumefantrine. Treatment response was monitored for 28 days using weekly microscopy screenings of blood samples for *P falciparum*. Mutations in *Pfkelch13* and *P falciparum* multidrug resistance-1 (*Pfmdr1*) genes were characterised in parasites collected from enrolled participants. Analysis of flanking microsatellites surrounding *Pfkelch13* was done to define the origins of the R561H mutations. The primary endpoint was PCR-corrected parasitological cure on day 28, as per WHO protocol.

Findings 228 participants were enrolled and 224 (98·2%) reached the study endpoint. PCR-corrected efficacies were 97·0% (95% CI 88–100) in Masaka, 93·8% (85–98) in Rukara, and 97·2% (91–100) in Bugarama. *Pfkelch13* R561H mutations were present in 28 (13%) of 218 pre-treatment samples and P574L mutations were present in two (1%) pre-treatment samples. 217 (90%) of the 240 *Pfmdr1* haplotypes observed in the pretreatment samples, had either the NFD (N86Y, Y184F, D1246Y) or NYD haplotype. Eight (16%) of 51 participants in Masaka and 12 (15%) of 82 participants in Rukara were microscopically positive 3 days after treatment initiation, which was associated with pre-treatment presence of *Pfkelch13* R561H in Masaka (p=0·0005). Genetic analysis of *Pfkelch13* R561H mutations suggest their common ancestry and local origin in Rwanda.

Interpretation We confirm evidence of emerging artemisinin partial resistance in Rwanda. Although artemether–lumefantrine remains efficacious, vigilance for decreasing efficacy, further characterisation of artemisinin partial resistance, and evaluation of additional antimalarials in Rwanda should be considered.

Funding The US President's Malaria Initiative.

Introduction

Artemisinin-based combination therapies (ACTs) are currently the most effective and widely used treatments for uncomplicated malaria caused by *Plasmodium falciparum*.[1] ACTs combine artemisinin derivatives, short-acting drugs that clear most of the parasite biomass within 3 days of treatment initiation, with long-acting partner drugs clearing the remaining parasitaemia. In 2006, Rwanda introduced artemether–lumefantrine combination therapy as the first-line treatment for uncomplicated malaria.[2]

WHO recommends therapeutic efficacy studies (TES) at least every 2 years for monitoring the efficacy of ACTs and the tracking of resistance through molecular markers.[3] When ACT efficacy is confirmed to be below 90% based on adequate clinical and parasitological response (ACPR) during an observation period (28 days or 42 days, depending on the partner drug), WHO recommends further confirmation and replacement with an effective antimalarial.[1] A TES using artemether–lumefantrine in Rwandan children aged 1–14 years was done between 2013 and 2015 in Ruhuha and Masaka, and the PCR-adjusted ACPR on day 28 was more than 97% in both sites.[4]

Partial resistance to the artemisinin component of ACT is suspected if delayed parasite clearance, defined as the

Research in context

Evidence before this study

We searched PubMed, without language restrictions, for articles published after 2005 using the terms "artemisinin", "ACTs", "resistance", "kelch 13" in combination with either "Africa" or "Rwanda". Artemisinin-based combination therapies (ACTs), introduced in the early 2000s, are the primary drugs used to treat uncomplicated malaria caused by *Plasmodium falciparum*. Evidence for artemisinin partial resistance was first reported in 2008 in Cambodia and subsequently confirmed in other parts of southeast Asia. Artemisinin partial resistance is characterised by delayed parasite clearance as shown by microscopically detectable parasitaemia on day 3 after treatment initiation. Despite artemisinin partial resistance, the efficacy of ACTs remains high until resistance to the partner drugs occur. Accumulation of mutations in the *P falciparum kelch 13* (*Pfkelch13*) gene have been associated with artemisinin partial resistance. Rwanda introduced artemether–lumefantrine as the first-line treatment of malaria in 2006. Past therapeutic efficacy studies (TES) in Rwanda found that artemether–lumefantrine had more than 90% efficacy. However, a *Pfkelch13* mutation in codon 561 (R to H transition) known to be associated with artemisinin partial resistance, was observed at low prevalence in studies from Rwanda, including a TES we did between 2013 and 2015. Additionally, reports in neighbouring countries, Uganda and Tanzania, have reported a low prevalence of this mutation. In the 2013–15 study, association of the mutation with day 3 parasitaemia was not found but the mutation was associated with increased survival rate expressed in vitro by the ring stage survival assay. Genomic analysis of the R561H isolates showed that the mutation had evolved independently in Rwanda.

Added value of this study

This 2018 TES showed that the overall efficacy of artemether–lumefantrine remained at more than 90%, but there was evidence of delayed parasite clearance, suggesting emergence of artemisinin partial resistance in Rwanda. Day 3 parasitaemia was observed in participants in two of the three sites and was associated with pre-treatment presence of the *Pfkelch13* R561H mutation in one site. Additionally, the prevalence of the *Pfkelch13* R561H mutation increased compared to previous reports. This is the first documented evidence of artemisinin partial resistance in Africa. Molecular analysis of *Pfkelch13* R561H mutant samples observed in our study support the previous observation of an independent evolution in Rwanda. There was no evidence of partner drug (lumefantrine) resistance, which is consistent with the more than 90% efficacy of artemether–lumefantrine observed.

Implications of all the available evidence

Emergence of artemisinin partial resistance in Africa is a warning signal that the efficacy of ACTs could become compromised should resistance to the partner drug emerge. These results highlight the importance of additional TESs to confirm the current findings and collect additional evidence for the presence of delayed parasite clearance by more frequent monitoring (every 8 h) of parasitaemia within the first 3 days following treatment. Additional molecular surveillance in different parts of the country and in bordering countries will help monitor the extent of spread of the mutant parasites to inform public health actions to mitigate the spread of this mutation. Periodic high-quality TESs are required to detect changes in the sensitivity of parasites to artemether–lumefantrine, which could affect national malaria treatment policy.

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persistence of parasitaemia on day 3 after treatment initiation, is observed.[1] First identified in Cambodia, artemisinin resistance is well documented in many southeast Asian countries[5–9] and is associated with parasites that have mutations in the *Pfkelch13* gene.[10] Ten single nucleotide polymorphisms in the *Pfkelch13* propeller domain have been validated as molecular markers of artemisinin partial resistance: F446I, N458Y, M476I, Y493H, R539T, I543T, P553L, R561H, P574L, and C580Y.[1] Additionally, several other mutations in this gene, referred to as candidate markers, have been identified, but additional evidence is required to validate their association with artemisinin partial resistance.[1]

The R561H mutation was observed in 7·4% of *P falciparum* parasites collected in Masaka, Rwanda, between 2013 and 2015[11] and in 4·5% of parasites collected in Huye district, Rwanda, in 2019.[12] Additionally, a low prevalence of the P574L mutation was reported in isolates collected in Masaka and Ruhuha (2013–15)[11,12] and in Huye (2015).[13] However, the presence of these mutations was not found to be associated with day 3 parasitaemia but with increased survival rate expressed in vitro by the ring stage survival assay.[11] Nevertheless, these findings are concerning because an increase in the prevalence of these mutations could result in more patients having delayed parasite clearance, which could lead to an increased risk of selection and spreading of partner drug-resistant parasites and eventual ACT failure.

The Malaria and Other Parasitic Diseases Division of the Rwanda Biomedical Center did a routine TES in 2018 as per a WHO recommendation to do periodic antimalarial efficacy monitoring. We report on these TES results, including day 28 efficacy, day 3 persistence of parasitaemia, and the presence of molecular markers of artemisinin partial resistance and tolerance to lumefantrine in the *Pfkelch13* and *P falciparum multidrug resistance-1* (*Pfmdr1*) genes.

Methods

Study design and participants

This open-label, single-arm, multicentre, therapeutic efficacy study (TES) was done in three health centres:

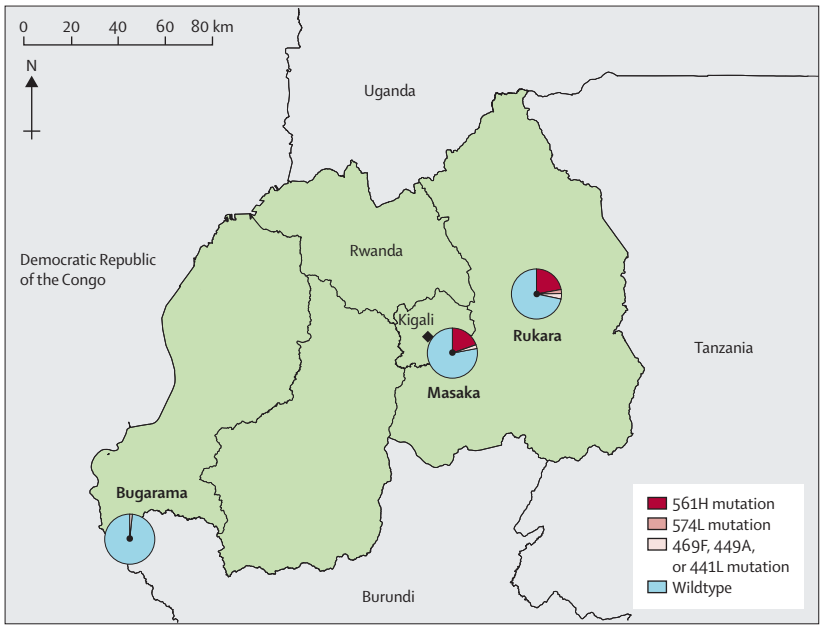

Figure 1: **Study sites and prevalence of *Pfkelch13* mutations in pre-treatment samples by study site**
This study was done in three Rwandan health centres: Rukara (Kayonza Distric), Masaka (Kicukiro District) and Bugarama (Rusizi District). The prevalence of the *Pfkelch13* R561H mutation was found in ten (20%) of 51 samples in Masaka, and eight (22%) of 82 in Rukara; that of the P574L marker was two (1%) of 82 samples in Rukara. Prevalence of the candidate artemisinin partial resistance markers was one (2%) of 51 samples in Masaka, three (4%) of 82 samples in Rukara, and one (1%) of 85 samples in Bugarama.

For the **WHO therapeutic efficacy study protocol** see https://www.who.int/malaria/areas/drug_resistance/efficacy-monitoring-tools/en/

Rukara (Kayonza district, Eastern Province), Masaka (Kicukiro district, Kigali Province), and Bugarama (Rusizi district, Western Province) (figure 1). Rukara and Bugarama have rural populations, and Masaka, located near the capital city Kigali, is an urban and peri-urban location with low transmission of malaria. These three sites were selected because they have varying transmission intensities and established study centres that have been used in previous TESs. In all three sites, *P falciparum* accounts for most malaria cases, with transmission seasons from May to July and November to December. Based on an assumption of 95% efficacy of artemether–lumefantrine, 95% CI, a precision of 10%, and 20% loss to follow-up, we estimated that 88 children needed to be enrolled per site.

Participants were eligible for enrolment if they were aged 6–59 months, had a fever at presentation (axillary temperature ≥37·5°C), history of fever in the past 24 h, or both, and parasitaemia of 1000–100 000 parasites per µL by microscopy. Other inclusion and exclusion criteria were assessed according to the standard WHO TES protocol.[3] Ineligible children were treated in accordance with national malaria treatment guidelines.[2]

This study was approved by the Rwanda National Ethics Committee (reference 195/RNEC/2017), Rwanda National Health Research Committee, and the Johns Hopkins Bloomberg School of Public Health Institutional Review Board. The US Centers for Disease Control and Prevention determined the laboratory work to be non-research (programme evaluation). Written informed consent was obtained from the parents or guardians of eligible children in the local language (Kinyarwanda).

Procedures

Microscopy screening

At each study site, potential participants were screened for malaria parasites using microscopy. Both thin and thick blood slides were prepared and stained with 5% Giemsa for 10–15 min and examined by two trained expert microscopists to detect and estimate density of malaria parasites. A blood slide was declared negative when examination of 100 high-power fields did not suggest the presence of *P falciparum* parasites.

Treatment and clinical monitoring during follow-up

Enrolled participants were admitted as inpatients and treated with a weight adjusted, six dose, 3-day course of artemether–lumefantrine (Coartem, Novartis). Each dose was given with water and fatty foods such as *ibitoki* (a local delicacy prepared from peanuts and bananas) to optimise bioavailability of the drug. Participants were observed for 30 min following administration of each dose to ensure they did not vomit. If vomiting occurred, a repeat dose was given after vomiting stopped. Parasitaemia was determined on the day of enrolment (day 0) and on days 2 and 3. Patients were discharged on day 3 after enrolment if they had a slide result that was negative for *P falciparum* malaria. Participants who were slide malaria positive on day 3 were kept in hospital until two consecutive malaria negative slides, prepared daily, were obtained. Treatment response was monitored for 28 days with scheduled visits on days 7, 14, 21, 28, and at any other time when patients were unwell (unscheduled visit). During every visit, clinical (evaluation of vital signs) and parasitological (malaria diagnosis by microscopy) assessments were done. Blood samples, for microscopy and preparation of dried blood spots on Whatman grade 3 filter papers (GE Healthcare Life Sciences, PA, USA), were collected from a finger prick. Patients with recurrent infections on day 7 and afterward were treated with quinine (tablets or injection) or artesunate injection (in patients with severe malaria), as per national treatment guidelines.[2]

DNA extraction and molecular analysis

Molecular analysis was done on all samples collected upon enrolment (pre-treatment samples) and during follow-up in the case of recurrent infections (post-treatment samples). Parasite genomic DNA was extracted from dried blood spots using a QIAamp DNA Mini Kit (Qiagen; Hilden, Germany). Molecular markers of antimalarial drug resistance and microsatellite markers were analysed by Rwandan laboratory technicians with support from US Centers for Disease Control and Prevention laboratory staff (Atlanta, GA, USA).[14] The *Pfkelch13* propeller domain (codon positions 440–600) and

Pfmdr1 (codon positions 86, 184, and 1246) were analysed for single nucleotide polymorphisms.[15,16] Sanger sequences were analysed using Geneious (version R11) software package (Biomatters; San Francisco, CA, USA) using the 3D7 *Pfkelch13* (PF3D7_1343700) and *Pfmdr1* sequences (PF3D7_0523000) as references. Raw sequence reads were cleaned using default settings and reads with high-quality scores (>30%) were further analysed.

Differentiation between recrudescence and reinfection

PCR correction, differentiating recrudescence from re-infection in recurrent infection samples, was done by genotyping seven neutral microsatellites (TA1 on chromosome 6, Poly-α on chromosome 4, *Pf*PK2 on chromosome 12, 2490 on chromosome 10, C2M34-313 on chromosome 2, C2M69-383 on chromosome 3, and TA109 on chromosome 6) in the paired pre-treatment and post-treatment samples. The sizes of the amplification products were determined by capillary electrophoresis on an Applied Biosystems 3130xl Genetic Analyzer (Applied Biosystems; Foster City, CA, USA). Microsatellite data were used to assign each recurrent infection a posterior probability of recrudescence using a Bayesian algorithm.[17] This analysis allowed for classification of recrudescent infections (if the posterior probability of recrudescence based on the algorithm was ≥50%) versus reinfections (<50% posterior probability) for tabulation. The posterior probabilities were used in the calculation of PCR-corrected per protocol and Kaplan-Meier estimates.

Pfkelch13 flanking microsatellite genotyping and genetic diversity

Seven microsatellite loci flanking the *Pfkelch13* gene on chromosome 13 (PF3D7_1343700; downstream of 3·4 kb, 8·6 kb, and 72·0 kb; upstream of –0·15 kb, –3·7 kb, –6·3 kb, and –31·9 kb) were used to characterise regions flanking *Pfkelch13* to assess for origin, genetic diversity, and patterns consistent with selection.[18] All isolates from Rwanda and four R561H mutant samples from Thailand were subjected to the *Pfkelch13* flanking sequence microsatellite analysis.[18] The heterozygosity on the flanking *Pfkelch13* microsatellites within each group (wildtype and mutant, in each population) was estimated using the Nei's index of genetic diversity (H_e).[19]

$$He=[n/(n-1)][1-\sum_{i=1}^{L} p_i^2]$$

n was obtained by taking the sum of identifiable alleles, and P_i was the relative frequency of the $_i$-th allele (i=1, . . . L) in all genotyped samples for each locus. H_e gave the average probability that a pair of alleles randomly selected from the population was different. Samples with mixed infections or missing data at any loci were excluded from the construction of the heterozygosity figure.

Outcomes

The primary endpoint was PCR-corrected parasitological cure on day 28 as per WHO protocol.[3] Secondary endpoints included parasitaemia on day 3 following treatment, which was assessed by microscopy and the prevalence of molecular markers of antimalarial drug resistance in *Pfmdr1* and *Pfkelch13* genes. Treatment outcomes were classified as early treatment failure (ie, development of signs of severe malaria, no rapid resolution of clinical symptoms, and slow clearance of slide parasitaemia), recurrent infections (ie, having detectable parasitaemia between day 4 and 28 during the follow-up) that included recrudescent infections and reinfections, or ACPR.[3]

Data management and statistical analysis

Data were entered into paper-based clinical record forms by trained staff at study sites, after which electronic double data entry was done at the national reference laboratory. Uncorrected and PCR-corrected per protocol[3] (proportional) and Kaplan-Meier (cumulative survival) estimates were calculated per site. Reinfections were calculated as the total number of recurrent infections minus the sum of the posterior probabilities of recrudescence among the recurrent infections and removed from the PCR-corrected per-protocol estimates. To calculate the Kaplan-Meier estimates and corresponding 95% CI, we did posterior sampling using the posterior probabilities of recrudescence. Prevalence of *Pfkelch13* mutations, *Pfmdr1* mutations, and *Pfmdr1* haplotypes were described by treatment outcome and site. Comparison analyses were done using Fisher's exact test and adjusted comparisons using logistic regression. All possible haplotypes from mixed infections (both wildtype and mutants) were included in construction of the *Pfmdr1* haplotype. Differences in the heterozygosity between the wildtype and R561H mutant haplotypes were measured using Wright's F statistics ranging from 0 to 1, by which 0 represents no differentiation.[20]

Role of the funding source

The sponsor of the study had no role in the recruitment of subjects and implementation of the TES but provided technical assistance in data analysis, data interpretation, and the writing of the report. At least five authors, including the corresponding authors had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Of 986 children screened at the three sites, 228 children with symptomatic uncomplicated *P falciparum* malaria were enrolled: 88 (39%) in Rukara, 52 (22%) in Masaka, and 88 (39%) in Bugarama. Lower than expected number of participants were enrolled in Masaka, probably because Masaka is located in a low transmission peri-urban site.

	Rukara	Masaka	Bugarama	Total
Baseline characteristics				
Enrolled, n	88	52	88	228
Age, years	2·9 (1·1)	3·1 (1·1)	3·2 (1·0)	3·1 (1·1)
Gender				
Male (%)	47 (53%)	23 (44%)	41 (47%)	111 (49%)
Female (%)	41 (47%)	29 (56%)	47 (53%)	117 (51%)
Weight, kg	13 (2·6)	13·8 (2·5)	13·3 (2·5)	13·3 (2·5)
Height, cm	86·5 (9·7)	92·6 (11·3)	93·9 (11·1)	90·7 (11·1)
Parasite density, parasites per µl at enrollment, median (range)	44 560 (1120–99 920)	41 440 (1160–99 200)	39 100 (1080–98 480)	42 760 (1080–99 920)
Treatment outcomes				
Early treatment failure	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Recurrent infections	21 (24%)	2 (4%)	14 (16%)	37 (16%)
Recrudescence	4 (19%)	2 (100%)	2 (14%)	8 (22%)
Days 8–14	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Days 15–21	4 (100%)	1 (50%)	2 (100%)	7 (88%)
Days 22–28	0 (0%)	1 (50%)	0 (0%)	1 (13%)
Reinfection	17 (81%)	0 (0%)	12 (86%)	29 (78%)
Days 4–7	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Days 8–14	1 (6%)	0 (0%)	1 (8%)	2 (7%)
Days 15–21	10 (59%)	0 (0%)	5 (42%)	15 (52%)
Days 21–28	6 (35%)	0 (0%)	6 (50%)	12 (41%)
ACPR	65 (74%)	48 (92%)	74 (84%)	187 (82%)
Excluded* or lost to follow-up	2 (2%)	2 (4%)	0 (0%)	4 (2%)

Baseline characteristics data are mean (SD) unless otherwise stated. ACPR=adequate clinical and parasitological response. *Three patients excluded between days 4–6 because they received additional antimalarial treatment.

Table 1: **Baseline characteristics of participants and classification of treatment outcomes**

	Kaplan-Meier		Per protocol	
	Uncorrected (95% CI)	PCR-corrected (95% CI)	Uncorrected (95% CI)	PCR-corrected (95% CI)
Rukara (n=88)	75·6% (68–85)	94·5% (90–100)	75·6% (65–84)	93·8% (85–98)
Masaka (n=52)	96·0% (91–100)	97·0% (93–100)	96·0% (86–100)	97·0 % (88–100)
Bugarama (n=88)	84·1% (77–92)	97·6% (91–100)	84·1% (75–91)	97·2% (91–100)

Data from follow-up at day 28.

Table 2: **Uncorrected and PCR-corrected Kaplan-Meier and per-protocol estimates of artemether–lumefantrine efficacy**

Baseline characteristics and treatment outcomes of participants are shown in table 1. Four (2%) of the 228 participants withdrew, three between days 4 and 6, and one on day 28. Only the participants who reached the study endpoints (224 [98%] of 228 participants) were included in the per-protocol analysis (table 1). No early treatment failures were observed, and no medication-related serious adverse events occurred. 37 recurrent infections were observed and 187 (84%) of 224 patients had ACPR. Of the recurrent infections, eight (22%) of 37 were classified as recrudescent infections and 29 (78%) of 37 as reinfections (table 1). The per-protocol PCR-corrected drug efficacies were 93·8% (95% CI 85–98) in Rukara, 97·0% (95% CI 88–100) in Masaka, and 97·2% (95% CI 91–100) in Bugarama. The uncorrected and PCR-corrected efficacies per study site are summarised in table 2 and appendix 2 p 1).

See Online for appendix 2

The *Pfkelch13* gene was successfully sequenced from 254 (96%) of 265 samples (218 pre-treatment and 36 post-treatment: 28 from reinfected patients and eight patients with recrudescent infections). 38 (15%) of 254 samples had the validated artemisinin partial resistance marker, of which 36 had a R561H mutation and two had a P574L mutation. Eight of the 36 isolates with the R561H marker were mixed infections (with wildtype and mutant strains). The R561H mutation was found in 28 (12·8%) of 218 pre-treatment samples, four (14·3%) of 28 reinfection samples, and four (50·0%) of eight recrudescent samples. Three candidate artemisinin partial resistance markers were found in six isolates: C469F in three isolates

	Day 3 parasitaemia positive		Day 3 parasitaemia negative	
	561H mutation	R561 wildtype	561H mutation	R561 wildtype
Rukara (n=82)	5 (6·1%)	7 (8·5%)	13 (15·9%)	57 (69·5%)
Masaka (n=51)	6 (11·8%)	2 (3·9%)	4 (7·8%)	39 (76·5%)
Bugarama (n=85)	0 (0·0%)	0 (0·0%)	0 (0·0%)	85 (100%)

Data are n (%). *Pfkelch13*=*Plasmodium falciparum kelch 13*.

***Table 3*: Prevalence of day 3 parasitaemia and *Pfkelch13* R561H mutation in pre-treatment isolates in the three study sites**

	–31·9 kb	–6·3 kb	–3·7 kb	–0·15 kb	3·4 kb	8·6 kb	72·0 kb
Rwanda							
Haplotype 1 (n=8)	209	277	152	194	128	262	236
Haplotype 2 (n=8)	209	277	150	194	128	262	236
Haplotype 3 (n=1)	197	277	150	194	128	262	236
Haplotype 4 (n=1)	209	271	152	194	128	262	236
Haplotype 5 (n=1)	209	277	150	194	128	262	232
Haplotype 6 (n=1)	209	277	152	194	132	262	236
Haplotype 7 (n=1)	219	277	152	194	128	262	236
Haplotype 8 (n=1)	209	277	150	194	120	278	232
Haplotype 9 (n=1)	209	277	150	194	128	262	252
Haplotype 10 (n=1)	209	277	152	194	128	262	232
Thailand							
Haplotype 1 (n=2)	203	283	148	194	130	288	230
Haplotype 2 (n=1)	203	283	148	194	130	288	244
Haplotype 3 (n=1)	203	283	148	194	130	288	250

Data represent the sizes, in base pairs, of the flanking microsatellites surrounding the *Pfkelch13*. This analysis showed ten similar haplotypes in the isolates from Rwanda. By contrast, different haplotypes were observed in the R561H isolates from Thailand.

***Table 4: Pfkelch13*-linked microsatellite haplotypes from Rwanda and Thailand**

(two pre-treatment and one recrudescence), P441L in one pre-treatment isolate, and G449A in two pre-treatment isolates. Additional *Pfkelch13* mutations, not known to be associated with artemisinin resistance, were observed in four isolates in Rukara: V555A (three isolates) and R575K (one isolate). The prevalence of the *Pfkelch13* mutants associated with artemisinin partial resistance was determined per site in pre-treatment isolates (figure 1).

A total of 243 (95%) of 255 samples were successfully sequenced in the *Pfmdr1* gene: 208 pre-treatment and 35 post-treatment (appendix 2 p 4). The N86Y, Y184F, D1246Y (NYD) haplotype was observed in 114 (48%) of 240 of pre-treatment and 20 (50%) of 40 post-treatment and the N86, 184F, D1246 (NFD) haplotype was observed in 103 (43%) of 240 of pre-treatment and 16 (40%) of 40 of post-treatment total observed haplotypes (appendix 2 p 4). No difference was seen in the prevalence of the NFD and NYD haplotype in participants with recrudescent infection (eight [100%] of eight) compared with those with ACPR, (177 [91%] of 194; Fisher's exact test, p=1·00).

A total of 20 participants (eight of [16%] 51 participants in Masaka and 12 [15%] of 82 participants in Rukara) had detectable parasitaemia by microscopy on day 3 post-treatment, a WHO criterion for artemisinin partial resistance.[1] 11 (55%) of these 20 participants also carried the R561H mutation (table 3). Presence of day 3 parasitaemia was compared between pre-treatment samples with (n=28) and without (n=190) the R561H mutation. Day 3 parasitaemia was observed in 11 (39%) of isolates with the R561H mutation and in nine (5%) of 190 isolates without the mutation (Fisher's exact test, p<0.0001). When adjusting for initial parasitaemia, the association between day 3 parasitaemia and presence of the R561H mutation remained (adjusted OR 14·2, 95% CI 5·1–41·5, p<0·0001). When stratified by site, this association was only observed in Masaka (p=0.0005) and not in Rukara (p=0·063). Two pre-treatment isolates had the P574L mutation, one from Masaka and one from Rukara, neither of which had day 3 parasitaemia and both were classified as ACPR. Three of the five pre-treatment isolates with the candidate mutations, (one with C469F and two with G449A), all from Rukara, also had day 3 parasitaemia; however, additional association analyses were not done because of the small sample size.

To determine whether *Pfkelch13* R561H mutation was associated with the 28-day treatment outcome, proportions of pre-treatment isolates with this mutation were compared in participants with parasite clearance with those who were classified as having

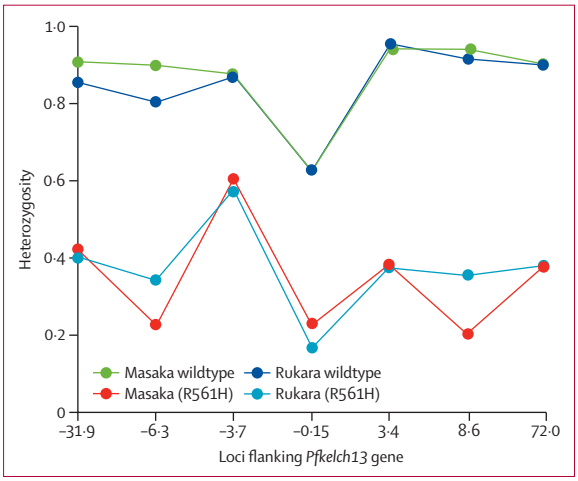

***Figure 2*: Reduced heterozygosity on the sampled loci around the *pfk13* gene in R561H isolates**

A total of 33 R561H mutations (nine from Masaka and 24 from Rukara) and 49 wildtype isolates (24 from Masaka and 25 Rukara) are shown (samples with mixed infections or missing data at any loci were excluded). We observed distinct haplotypes with the R561H mutation (compared with the wildtype (blue and green lines), with a reduction in the heterozygosity in those with the R561H mutation. The heterozygosity of the wildtype genotypes was significantly different and higher than the one observed in the sympatric R561H mutant haplotypes in the two populations.

recrudescent infection. Samples from four (50%) of eight participants with a recrudescent infection had a mutation compared with samples from 22 (12·4%) of 178 participants with parasite clearance (Fisher's exact test, p=0·014).

Analysis of flanking microsatellites surrounding *Pfkelch13* was investigated in 82 isolates (33 R561H mutants and 49 R561H wildtypes). Recrudescent infections and isolates with multiple infections were excluded in the haplotype analysis. The sizes of the microsatellites were considered unique if they differed by two base pairs except for the –6·3 kb locus, for which a difference in three base pairs was used. Similar haplotypes, differing only in a few loci, were observed in the R561H mutation from Rwanda, which were different from haplotypes observed in the R561H mutation from Thailand (table 4, appendix 2 p 5). Genetic diversity in the R561H mutant, as estimated by the heterozygosity on the flanking *Pfkelch13* microsatellites, was lower than that observed in wildtype parasites (figure 2). Wildtype genotypes were highly differentiated from their sympatric R561H mutation in both populations (average *F* 0·847 between the R561H wildtype and R561H mutation in Masaka, p=0·0021; *F* 0·841 in Rukara, p=0·0006).

Discussion

This study confirms that artemether–lumefantrine remains highly efficacious in all three study sites, with PCR-corrected efficacy of 94–97%. However, the presence of two validated markers of artemisinin partial resistance, R561H and P574L, and delayed parasite clearance (parasitaemia at day 3) in more than 10% of the study participants in Masaka and Rukara are of some concern.[1] Although factors such as initial parasitaemia on admission are known to affect parasite clearance rate,[21] treatment with artemisinin compounds results in a rapid clearance of parasitaemia by day 3 of treatment initiation, and delayed parasite clearance is suggestive of artemisinin partial resistance.[1,5] The prevalence of the *Pfkelch13* R561H mutation was significantly higher in patients with recrudescent infections than in those who cleared their infection, and the association between day 3 parasitaemia and presence of the R561H mutation was significant in Masaka. However, besides artemisinin partial resistance, other factors affecting treatment efficacy include efficacy of the partner drug, host immunity, and drug absorption. These factors could explain why R561H mutations were also observed in patients who cleared their infections and the fact that the association between day 3 parasitaemia and having the R561H mutation was significant in Masaka but not in Rukara.

Results from our study confirmed the previous finding of *Pfkelch13* R561H mutations in isolates collected in Masaka, Rwanda, between 2013 and 2015.[11] The prevalence of *Pfkelch13* R561H mutation in our study was found to be higher than previously reported in Rwanda,[11,12] Uganda,[22] and Tanzania,[23] suggesting that this mutation is strongly selected for in Rwanda. It remains to be determined if other detected mutations, such as *Pfkekch13* P574L mutations, will be selected for and increase over time. P574L mutations have also been shown to confer artemisinin resistance using in-vitro susceptibility assays, albeit to a lesser degree by comparison with the R561H mutation.[11]

Further investigation into the origin of *Pfkelch13* R561H mutations using *Pfkelch13* flanking microsatellite analysis revealed that they shared similar haplotypes distinct from *Pfkelch13* R561H haplotypes observed in Thailand. Similar results were obtained, using a whole-genome sequencing (WGS) analysis for the R561H isolates collected in 2012–15 from Rwanda.[11] Together, these results suggest an independent origin of the *Pfkelch13* R561H mutation in Rwanda.[11] Microsatellite analysis has been used for similar analyses in previous evaluations,[24] including landmark studies on the evolution of chloroquine[25] and sulfadoxine resistance.[26] Although microsatellites are less powerful than WGS, they provide a good alternative, particularly when appropriate samples for WGS are not available, as was the case in this study.

As previously reported in Africa,[12,27] we identified the candidate markers *Pfkelch13* C469F, P441L, and G449A and two additional mutations, V555A and R575K, whose role in artemisinin partial resistance is unknown. Studies have also detected mutations beyond codon 600 such as A675V,[22] which our study did not examine. To date, the reported prevalence of the aforementioned mutations in Africa is low, however, a study showed that the prevalence

of C469Y and A675V mutations has increased at multiple sites in northern Uganda (up to 23% for C469*Y* and 40% for A675V).[22] Therefore, monitoring of these mutations in Africa is important even if the efficacy of most of the commonly used ACTs is high. It is possible that other *Pfkelch13* mutations observed in African isolates but not validated so far, or mutations in other unknown genes, will affect artemisinin resistance in Africa, but this hypothesis will have to be determined by additional studies on the continent.

Most samples in this study had either the NFD or NYD haplotype of the *Pfmdr1* gene, associated in some studies with decreased sensitivity to lumefantrine.[28] The prevalence of these two *Pfmdr1* haplotypes in this study was similar in a 2011 study, in which 59% of the *P falciparum* isolates collected in a southern province of Rwanda had those haplotypes.[29] In our study, the NFD and NYD haplotypes were highly present in pre-treatment isolates and did not appear to be selected in post-treatment isolates; despite this high prevalence, their presence in pre-treatment isolates was not associated with recrudescent infections.

Efficacy of artemether–lumefantrine remains high in Rwanda despite the presence of *Pfkelch13* mutations and delayed parasite clearance. In general, ACTs remain efficacious even if artemisinin partial resistant mutations are present as long as the partner drug is still effective. Evidence from the Mekong region has shown that once artemisinin resistance becomes prevalent, resistance to the partner drug often follows, resulting in ACT treatment failure.[30] Additional studies, including parasite clearance assays within the first 3 days of treatment, in-vitro assays to determine mutant parasites' phenotypes, and WGS to determine relatedness of mutant parasites, will further confirm our findings in Rwanda. Heightened vigilance for artemether–lumefantrine efficacy and the evaluations of the efficacy of other ACTs in Rwanda should be considered.

Contributors

AU, NU, EF, KM, WB, MM, MV, and EH designed and planned the study. AU, NU, AM, DN, AR, JLM, CM, and LM coordinated and supported all the field operations of the study. RMH, TM, SS, BE, IG, prepared the sample inventories, performed the molecular assays and data processing. ET, NWL, ZZ, and VU supervised the molecular assays and data processing and interpretations. MAP and AE did the microsatellite data analysis. LFM, MK, RS, NWL, and MV provided statistical analysis support. AU, NWL, EH, VU, and AM supervised the study including analysis, interpretation, and writing of the Article. All authors read and revised the manuscript and agreed to the final version. AU, LFM, VU, EH and NWL had access to and verified the data.

Declaration of interests

We declare no competing interests.

Data sharing

All data will be made available upon reasonable request after publication.

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RESEARCH ARTICLE

Recent infections among individuals with a new HIV diagnosis in Rwanda, 2018–2020

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Abstract

Background

Despite Rwanda's progress toward HIV epidemic control, 16.2% of HIV-positive individuals are unaware of their HIV positive status. Tailoring the public health strategy could help reach these individuals with new HIV infection and achieve epidemic control. Recency testing is primarily for surveillance, monitoring, and evaluation but it's not for diagnostic purposes. However, it's important to know what proportion of the newly diagnosed are recent infections so that HIV prevention can be tailored to the profile of people who are recently infected. We therefore used available national data to characterize individuals with recent HIV infection in Rwanda to inform the epidemic response.

Methods

We included all national-level data for recency testing reported from October 2018 to June 2020. Eligible participants were adults (aged ≥15 years) who had a new HIV diagnosis, who self-reported being antiretroviral therapy (ART) naïve, and who had consented to recency testing. Numbers and proportions of recent HIV infections were estimated, and precision around these estimates was calculated with 95% confidence intervals (CI). Logistic regression was used to assess factors associated with being recently (within 12 months) infected with HIV.

Results

Of 7,785 eligible individuals with a new HIV-positive diagnosis, 475 (6.1%) met the criteria for RITA recent infection. The proportion of RITA recent infections among individuals with newly identified HIV was high among those aged 15–24 years (9.6%) and in men aged ≥65 years (10.3%) compared to other age groups; and were higher among women (6.7%) than men (5.1%). Of all recent cases, 68.8% were women, and 72.2% were aged 15–34 years. The Northern province had the fewest individuals with newly diagnosed HIV but had the

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highest proportion of recent infections (10.0%) compared to other provinces. Recent infections decreased by 19.6% per unit change in time (measured in months). Patients aged ≥25 years were less likely to have recent infection than those aged 15–24 years with those aged 35–49 years being the least likely to have recent infection compared to those aged 15–24 years (adjusted odds ratio [aOR], 0.415 [95% CI: 0.316–0.544]).

Conclusion

Public health surveillance targeting the areas and the identified groups with high risk of recent infection could help improve outcomes.

Introduction

Considerable progress has been made to contain the HIV epidemic globally. However, data reported from the Joint United Nations Programme on HIV/AIDS (UNAIDS) show the need to keep the momentum to achieve sustainable epidemic control by 2030 [1, 2]. New HIV infections have decreased globally, due in part to scale-up of antiretroviral therapy (ART) coverage, early ART initiation and retention of individuals with new HIV diagnoses, and viral load (VL) suppression, which help decrease transmission rates [3, 4].

Despite this progress, in 2017, an estimated 14.5 million people had undiagnosed HIV infection [5]. To address this gap, new strategies, including active case finding and recency testing, were integrated in many country programs with limited HIV-testing resources to identify high-risk individuals with undiagnosed HIV infections and help routinely detect and interrupt HIV transmission networks to achieve epidemic control. In 2018, Rwanda adopted recency testing to monitor what percentage of the newly diagnosed HIV positives was recent. This was intended to inform HIV prevention and HIV testing to target people who are likely to acquire and transmit HIV [6]. Recency testing with limiting-antigen avidity assays is used in some African countries to estimate HIV incidence and has been proven to be cost-effective in estimating new infections to inform the public health response [7]. New HIV infections in Rwanda previously have been estimated using mathematical modeling from the Estimation and Projection Package-Spectrum and cohort-based surveys [8]. Recency testing could be another method to estimate HIV incidence in other countries, including Rwanda. It may also be useful for index testing and finding partners who may also be recently infected but it is not intended for the diagnosis of HIV infection.

Despite Rwanda's Progress toward HIV epidemic control, 16.2% of HIV-positive individuals are unaware of their HIV positive status [9]. Tailoring the public health strategy could help reach these individuals with new infection and achieve epidemic control. In 2018, the Rwanda Ministry of Health and its partners launched a 5-year strategic plan to address new HIV infections to help the country achieve and sustain HIV epidemic control [10]. In October 2018, Rwanda introduced laboratory methods used to detect and confirm recent infections among individuals with a new HIV diagnosis within the last 12 months [7]. These new approaches have helped the government of Rwanda to increase awareness of HIV status among PLHIV, to enhance timely linkage to care and treatment, and to stop transmission under the case-based surveillance program. This approach has helped map new HIV infections and characterize individuals at high risk of infection to develop tailored prevention measures to stop HIV transmission. In this study, we used data from the Recency Web application to evaluate the progress

made in identifying recent HIV infections and identify risk factors associated with recent HIV infection.

Methods

Study design

Our retrospective cross-sectional study used recency testing data collected through the Rwanda National Health Information System (October 2018–June 2020). Recency data are collected using an electronic system called the Recency Application (known as the Recency App) and Laboratory Information Management System (Web LIMS/LabWare). The system also collects data on patient identification, quality control, demographic information including age and Sex, and health facility information. Collected information is uploaded into the Recency App and Web LIMS/LabWare, and a countrywide dataset was exported for our analysis.

Data collection

Clients with HIV-positive results from voluntary counselling and testing services, out-patient departments, antenatal care, voluntary medical male circumcision program, internal patient departments, and prevention of mother-to-child HIV transmission program are screened for eligibility for recency testing. Our analysis included patients aged ≥15 years with a new HIV diagnosis made during the study period (October 2018–June 2020) and, self-reported that they had never initiated ART. Participants provided verbal informed consent (materials were written in English and were translated into Kinyarwanda, the local language). Clients who did not provide informed consent received HIV care and treatment, per national guidelines.

Laboratory testing

The Asante rapid HIV-1 recency test assay based on limited antigen and antibody avidity was used to perform recency testing on clients with newly diagnosed HIV-1 who were aged ≥15 years and who had received counselling and had given informed consent before initiating ART. Whole-blood samples were collected from eligible clients at primary health care facilities. Rapid recency tests were performed, per the recency testing standard operating procedure, by trained laboratory staff at primary health care facilities or at VL testing hubs (e.g., the Rwanda National Reference Laboratory) located across the country. According to the Asante assay, the duration of infection flagged as recent is ≤12 months. The False Recency Rate (FRR) was estimated to be about 1% excluding treated patients and elite controllers [11]. Additional recent validation of the assay to generate more data in specimens from individuals of known duration of infection have shown a very high specificity but lower sensitivity in Uganda [12] and very high for both in Vietnam [13]. Long-term infection results were immediately returned to the participants, and all samples identified as recent infection via Asante underwent additional testing for VL, per the Recent Infection Testing Algorithm (RITA) in Rwanda (Fig 1). Pre- and post-test counseling on what 'recent infection' means and implication of recency results for their own health as well as health of sexual partners was provided to all participants classified as recent.

VL testing was conducted using Roche COBAS AmpliPrep/COBAS TaqMan HIV-1 for plasma samples. Samples with VL ≥1000 copies/mL were confirmed as recent infection, and those with <1000 copies/mL were reclassified as long-term infections. RITA results were returned to the health facility within 14 days. Results confirming recent infection and VL were returned to the client.

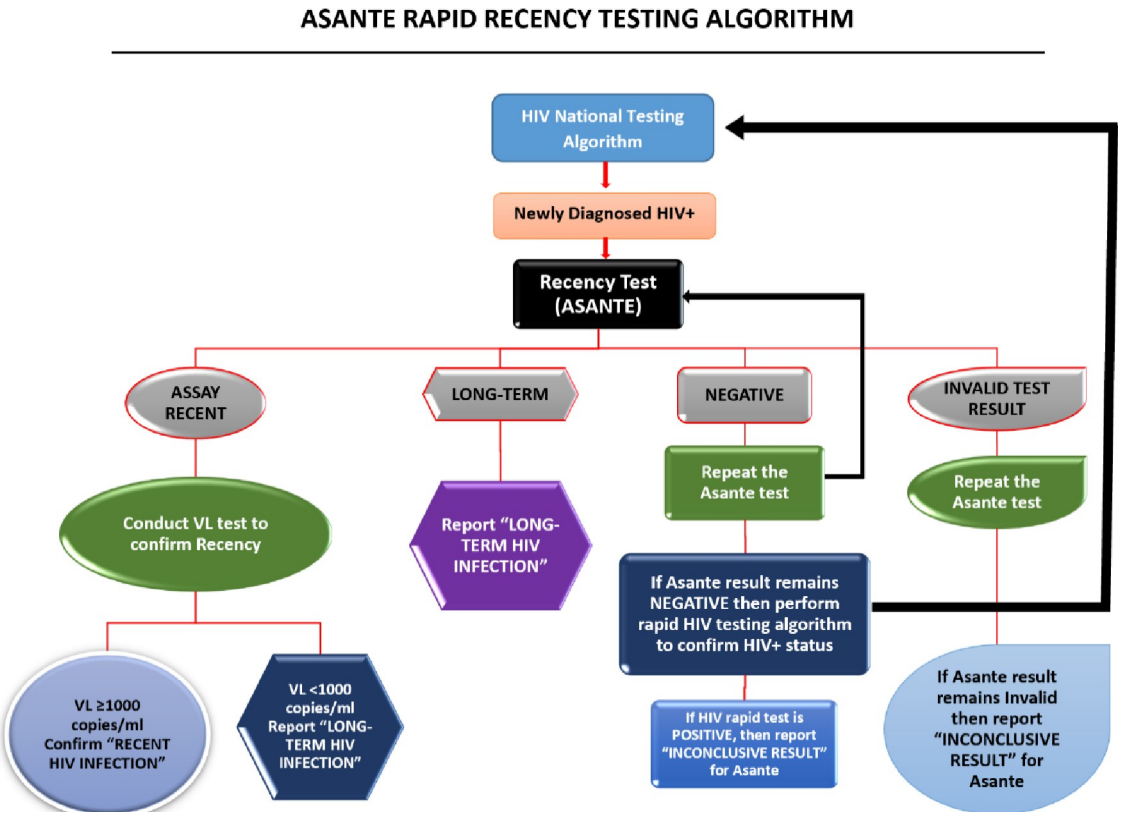

Fig 1. The Asante Rapid Test and Recent Infection Testing Algorithm (RITA).

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All laboratory test results, including quality control and individual sample testing, were recorded in the laboratory records and uploaded into the Recency App and LIS, respectively. The National Reference Laboratory periodically reviews completed data from testing sites and reporting to the program for surveillance and continuous quality improvement at health facilities.

Ethical consideration

Recency testing was approved under the Active Case-Based Surveillance for HIV in Rwanda protocol. The program was reviewed and approved by the Rwanda National Ethics Committee. It was also reviewed in accordance with CDC human research protection procedures and was determined to be research, but CDC investigators did not interact with human subjects or have access to identifiable data or specimens for research purposes.

All eligible patients provided verbal informed consent before enrolling in the study. A waiver of parental consent and assent was received from the Rwanda National Ethic Committee for participants aged 15–17 years who provided verbal consent before enrollment into the program.

Statistical analysis

We determined the number of recent HIV infections among clients with newly diagnosed HIV, estimated and tested for the difference in proportions using chi-square test for bivariate comparison, and calculated 95% confidence intervals (CI). Logistic regression was used to

identify risk factors associated with recent HIV infection. Factors with $p \leq 0.1$ on univariate logistic regression were included in a full model using stepwise regression in which final explanatory variables were chosen automatically: in each step, a variable was considered for addition to or subtraction from this set of explanatory variables based on the prespecified criterion of including factors that were associated with recent HIV infections at $p < 0.05$ in the final multivariable logistic regression model.

All proportion estimates were weighted to account for non-acceptance to recency testing and reporting gaps among individuals with newly diagnosed HIV at the time of using the Recency App. A weight was calculated by taking the reciprocal of the proportion of all individuals with newly diagnosed HIV reported through the Recency App during the reporting period.

Time trends were analyzed using logistic regression with recent infection as a dependent variable and time in month as an independent variable. Multivariable logistic regression with recent infection as a dependent variable was fitted to measure the association between HIV recency and sex, key age groups, and provinces. Independent categorical variables included a missing value category to minimize list-wise deletion of observation in the models. Data were managed and analyzed using STATA, version 15.0 (College Station, TX).

Results

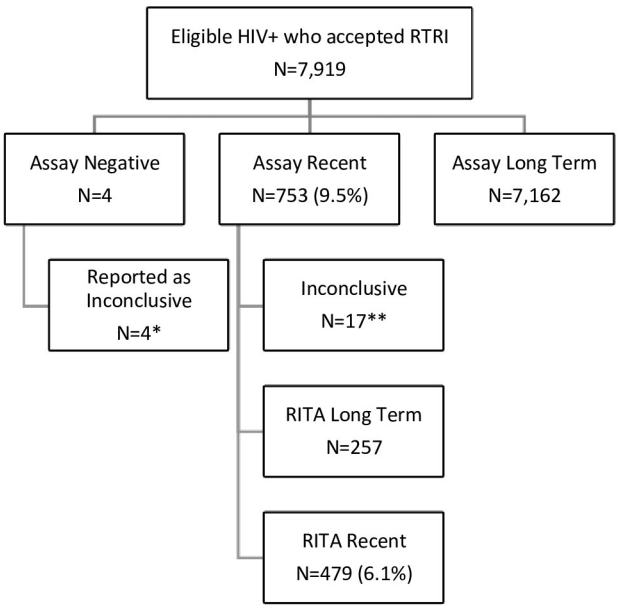
Between October 2018 and June 2020, a total of 1,845,061 samples were tested for HIV in the sites that were offering recency testing at the time, of which 1,834,360 (99.4%) tested HIV negative, and 10,701 (0.6%) tested HIV positive. Of the positive samples, approximately a quarter (2,782) were never tested for recency due to two main reasons, namely having no consent for recency testing, and finding evidence during the recency testing counseling sessions of prior exposure to antiretroviral drugs. A total of 7,919 samples (74%) were sent for recency assay testing, of which 753 tested assay recent, giving a proportion of assay recent infections of 9.5% (753/7919) but when recent infection was defined as assay recent together with a viral load (VL) $\geq$1,000 copies/mL (excluding the negative and, inconclusive sample results), only 6.1% (479/7898) of samples were classified as RITA recent infections (Fig 2).

The absolute number of recent infections among men and women were highest among women aged 15–34 years (259) and among men aged 25–49 years (108). The proportion of recent infections among newly identified positives was higher among women (6.7%) than men (5.1%) and highest in both men (10.0%) and women (9.5%) aged 15–24 years (Table 1). Though the number of samples tested was small, a high proportion (10.3%) of the newly identified HIV positive samples from men aged $\geq$65 years tested recent. Of all recent cases, 68.8% (327/475) were women, and 72.2% (343/475) were aged 15–34 years.

The pattern of newly diagnosed and recent HIV infections by province was similar between men and women, though the absolute number of recent infections was higher among women than men. For both men and women, the proportion of recent infections was highest in the Northern province, which had the lowest number of newly diagnosed HIV infections. The City of Kigali considered the fifth province and the capital city of Rwanda) had the highest numbers of newly diagnosed HIV infections (Fig 3).

Five of the top ten districts with the highest proportion of recent infections in newly diagnosed HIV infections were from the Northern Province (Fig 4A), and the three districts making up the City of Kigali had the highest number of absolute recent infections (Fig 4B).

The proportion of recent infections among individuals with newly identified HIV infection in Rwanda decreased, but the number of HIV-positive samples tested for recent infections increased over time (Fig 5).



*As per National Recent Infection Testing Algorithm (RITA), 4 samples were reported as inconclusive due to discrepancy between HIV testing algorithm and Assante rapid recency assay (Algorithm: Positive and Assante: Negative).

**17 Samples were reported as inconclusive due to failed viral load test.

Fig 2. Flow diagram of final HIV recency testing outcome by assay outcome in Rwanda (2018–2020).

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After adjusting for differences in sex, age, and province where samples with newly identified HIV infection were collected, we observed a significant decrease in individuals with recent HIV infection (5.2% per month; adjusted odds ratio [aOR], 0.948; Table 2).

Individuals with newly identified HIV aged 15–24 years were more likely to have recent infection than those aged 25–34 years (aOR = 0.625 [95% CI: 0.497–0.784]), 35–49 years (aOR = 0.415 [0.316–0.544]) and 50–64 years (aOR = 0.449 [95% CI: 0.290–0.694). Individuals with newly identified HIV from the Eastern Province were more likely to have recent infection than those from the Western Province (aOR, 0.527 [95% CI: 0.369–0.752]) or from the City of

Table 1. HIV RITA recency testing outcome by age and sex in Rwanda (2018–2020)*.

	Women			Men			Combined		
Age, years	Total	Long Term (%)	Recent (%)	Total	Long Term (%)	Recent (%)	Total	Long Term (%)	Recent (%)
15–24	1,338	1,211 (90.5)	127 (9.5)	259	233 (90.0)	26 (10.0)	1,597	1,444 (90.4)	153 (9.6)
25–34	1,999	1,867 (93.4)	132 (6.6)	1,110	1,052 (94.8)	58 (5.2)	3,109	2,919 (93.9)	190 (6.1)
35–49	1,203	1,154 (95.9)	49 (4.1)	1,206	1,156 (95.8)	50 (4.2)	2,409	2,310 (95.9)	99 (4.1)
50–64	297	279 (93.9)	18 (6.1)	272	264 (97.1)	8 (2.9)	569	543 (95.4)	26 (4.6)
65+	43	42 (97.7)	1 (2.3)	58	52 (89.7)	6 (10.3)	101	94 (93.1)	7 (6.9)
Total	4,880	4,553 (93.3)	327 (6.7)	2,905	2,757 (94.9)	148 (5.1)	7,785	7,310 (93.9)	475 (6.1)

*Age or sex were not recorded on 113 samples, (long-term, 105; recent, 8), 4 samples tested negative and 17 samples did not have a conclusive recency test result. They were therefore excluded from analysis and results presented in Table 1.

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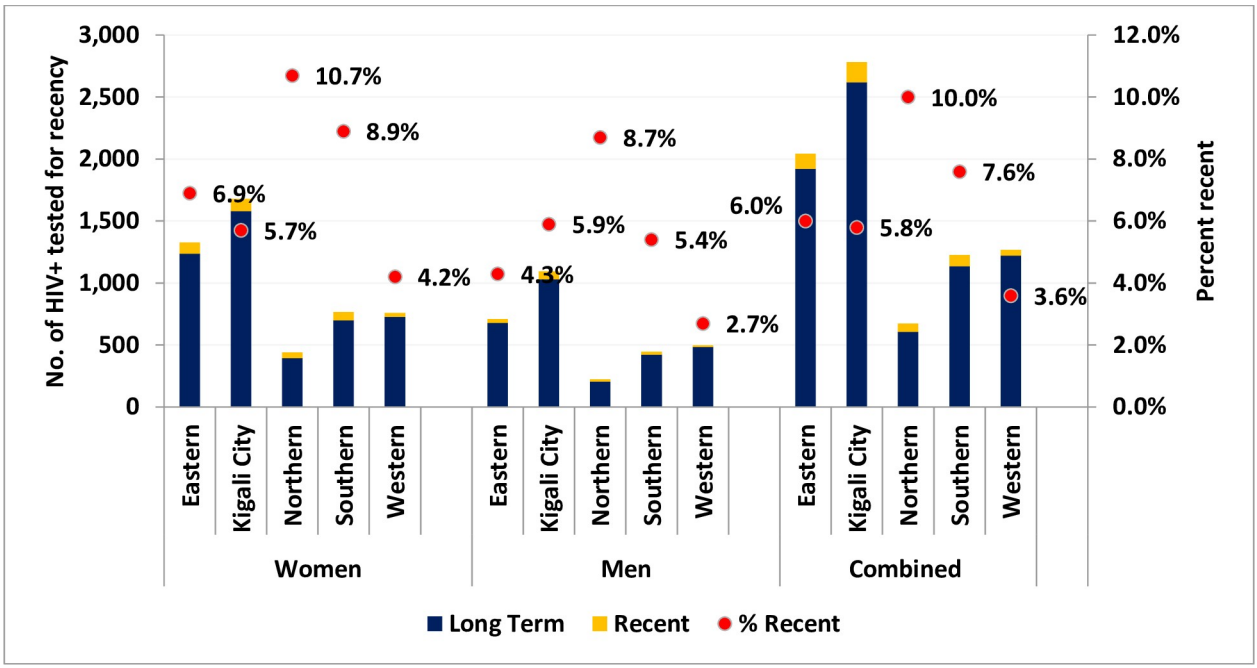

Fig 3. Newly diagnosed and recent HIV infections by province in Rwanda (2018–2020).

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Kigali (aOR, 0.761 [95% CI: 0.587–0.985]). HIV-positive individuals from the Northern Province were more likely to have a recent infection than those from the Eastern Province (aOR, 1.560 [95% CI: 1.133–2.147]), even though the Northern Province had the fewest number of individuals with newly identified HIV infections (Table 2).

Discussion

Our study is the first to analyze recency data 2 years after Rwanda launched recency testing to map and characterize new infections and inform public health strategies. We found that 6.1% of PLHIV with a new diagnosis had acquired this infection within the last 12 months of sample collection. This finding is similar to the recency rate reported in a feasibility study done in Kenya (8.6%) but is lower than rates reported in European studies that mainly focused on high-risk groups [14]. The limiting antigen avidity assay methods have been used to measure HIV incidence [7] however, the Asante rapid recency assay testing, though based on the same principle as the limiting antigen (LAg) avidity assay, was used for surveillance and monitoring trends of active transmission of HIV in the population and to inform epidemic response in Rwanda.

We found that the biggest number of recent infections were localized in the City of Kigali, compared to other provinces. The City of Kigali has more female sex workers and men who have sex with men than other provinces in Rwanda [15–17], and these key populations have higher HIV infection rates and more recent infections than in the general population. The City of Kigali also has the highest HIV prevalence (3.7%) in Rwanda compared to other provinces (Southern, 2.3%; Western, 2.8%; Northern, 1.8%; and Eastern, 2.5%) [9] and thus has high rates of transmission [8, 9]. The City of Kigali also may have had more recent infections because, as the pilot site before national implementation, health facilities in the City of Kigali received more mentorship to implement recency testing than other sites. The City of Kigali has a higher HIV-testing volume than other provinces because residents are more likely to get

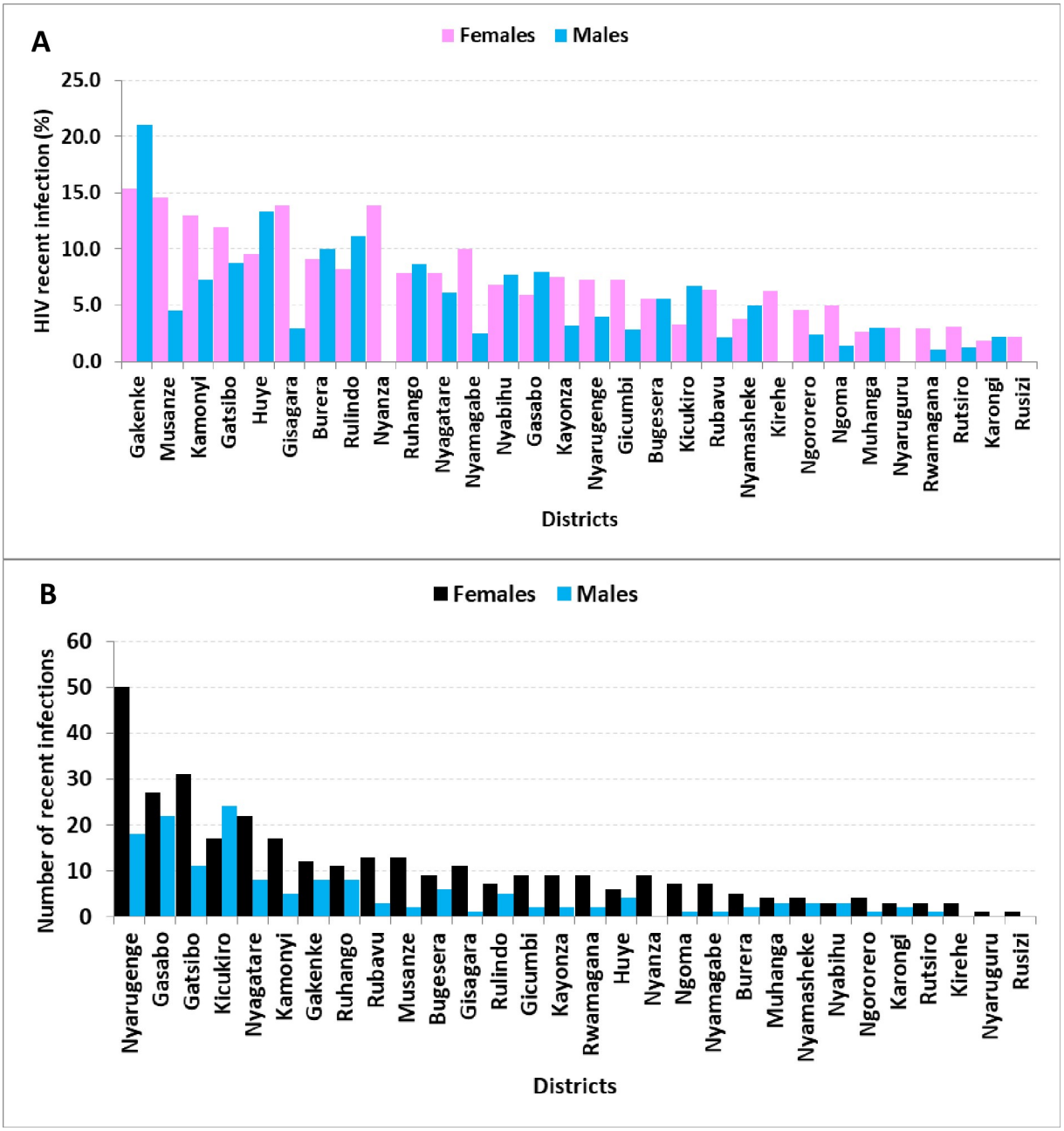

Fig 4. A. Indicating the final recent HIV infection proportions and B. Indicating the absolute number of recent HIV infections by district and sex in Rwanda (2018–2020).

https://doi.org/10.1371/journal.pone.0259708.g004

tested for HIV than Rwandans in other provinces due to more access to HIV-testing locations and education about HIV prevention [9].

Our finding that women represent 70% of the total HIV recent infections compared to men supports other reported data [18]. This finding might be explained by gender discrepancies in seeking healthcare services, by women's higher HIV acquisition risk, or imbalances in power in negotiating for safe sex. However, the odds of testing recent in females, was not statistically significant from that in males.

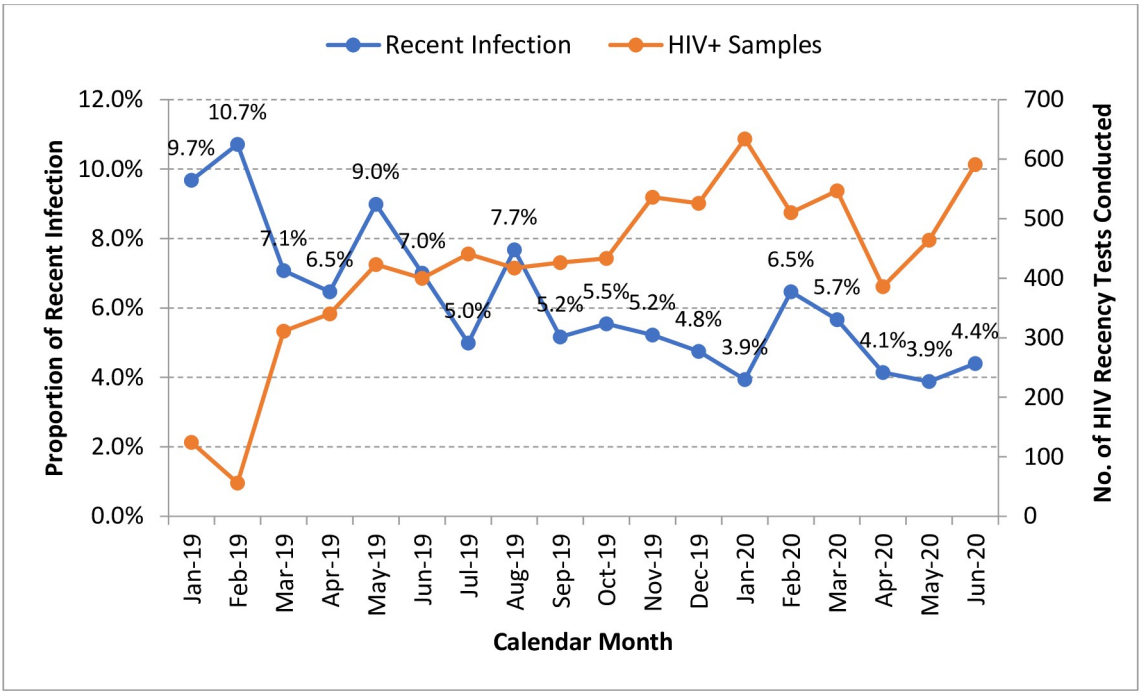

Fig 5. Proportion of recent infections per month among individuals with newly identified HIV infection in Rwanda (2018–2020).

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Our findings show that recent HIV infections were more frequent in women aged 15–34 years and among men aged 25–49 years. The odds of testing recent was lower among those aged ≥25 years compared to those aged 15–24 years. Similar findings have been reported in other studies where young women have the most recent infections [18]. In the 2018 Rwanda

Table 2. Univariable and multivariable logistic regression analysis of recent infection with sex, age, and province in Rwanda (2018–2020).

Variable	N = 7,785	No. RITA recent (%)	Unadjusted Odds Ratio	95% CI	p-value	Adjusted Odds Ratio	95% CI	p-value
Time in Quarters	7,785	475 (6.1%)	0.830	0.785–0.878	<0.001	0.804	0.757–0.853	<0.001
Sex								
Female	4,880	327 (6.7%)	1.000			1.000		
Male	2,905	148 (5.1%)	0.747	0.612–0.913	0.004	0.883	0.716–1.089	0.243
Age, years								
15–24	1,597	153 (9.6%)	1.000			1.000		
25–34	3,109	190 (6.1%)	0.614	0.492–0.767	<0.001	0.625	0.497–0.784	<0.001
35–49	2,409	99 (4.1%)	0.404	0.311–0.525	<0.001	0.415	0.316–0.544	<0.001
50–64	569	26 (4.6%)	0.452	0.295–0.693	<0.001	0.449	0.290–0.694	<0.001
≥65	101	7 (6.9%)	0.703	0.320–1.542	0.379	0.752	0.339–1.666	0.482
Provinces								
Eastern	2,014	120 (6.0%)	1.000			1.000		
City of Kigali	2,726	157 (5.8%)	0.965	0.756–1.232	0.773	0.761	0.587–0.985	0.038
Northern	650	65 (10.0%)	1.754	1.279–2.405	<0.001	1.560	1.133–2.147	0.006
Southern	1,175	89 (7.6%)	1.293	0.974–1.719	0.076	1.189	0.891–1.587	0.240
Western	1,220	44 (3.6%)	0.591	0.415–0.841	0.003	0.527	0.369–0.752	<0.001

* Samples with inconclusive recency test result were excluded from this analysis.

https://doi.org/10.1371/journal.pone.0259708.t002

Population-Based HIV Impact Assessment (RPHIA) survey, young women aged 20–24 years had the highest HIV prevalence, which was 3 times higher than men of the same age; the HIV prevalence was higher in men aged ≥50 years than in women of the same age group [9]. The results observed in this study and method of characterizing the recent HIV infection are in line with what was found elsewhere [6, 14, 18, 19].

Unlike the RPHIA results [9], our findings suggest that rural areas have a higher proportion of absolute number of recent infections, despite having lower testing rates, than urban areas. This observation may be related to an increase in recent HIV infections in other provinces compared to the City of Kigali, which aligns with RPHIA findings [9]. Another reason might be that rural areas (2.1%) in Rwanda have lower HIV prevalence than urban areas (4.1%), but urban areas have higher ART coverage and awareness of HIV-positive status than rural areas (indicated by the average number of people who know their HIV status and are receiving ART: urban, 80.2%; rural, 77.4%) [9]. The decrease in recent HIV infections to 5.2% after adjusting for age, sex, and province might have been due to scale-up of recency testing in rural health facilities with low HIV prevalence.

Recency testing is one of the strategies used in active case finding to detect new HIV transmission. In Rwanda, national guidelines recommend that every person with newly diagnosed HIV should be offered index testing and recency testing in addition to the standard of care. Studies conducted elsewhere revealed that new strategies such as active case finding can help individuals with a recent HIV-positive diagnosis to disclose their status to their partners and can increase the yields of the HIV-positive individuals who did not know their status and help them initiate ART [5, 20]. Additionally, contacts with HIV-negative results are counselled and linked to HIV prevention measures to maintain their HIV-negative serostatus [21].

Our study has several limitations. First, HIV recency testing is offered to individuals with a new HIV diagnosis; because only consenting individuals are tested for recency, our study sample does not include all individuals with a new HIV diagnosis. Second, Rwanda does not have a national unique identification system for HIV-positive individuals, so an individual with recent infection may be tested at different facilities and recorded more than once. However, because recency testing was offered only to individuals with a new HIV diagnosis, the number of repeat testers was small. Thirdly, some recent infections may have to be reclassified as long term if testing shows VL suppression, possibly because the client did not disclose their history of prior ART or is an elite VL controller. Lastly, ARV naivety was based on self-report as opposed to ART metabolite testing and this could have resulted in misclassification of recency by the assay.

We found that across all age groups, women had more absolute recent HIV infections than men. Individuals aged 15–34 years and men ≥65 years had a high prevalence of recent HIV infection. The City of Kigali had a higher rate of recent infections than other provinces. These findings warrant increased prevention interventions (e.g., HIV testing, condom distribution and education, and behavior change communication) targeting these individuals and introduction of pre-exposure prophylaxis among HIV-negative sexual partners of individuals with a new HIV diagnosis. Findings from this study showed that once integrated in routine HIV-testing services, recency testing can help map, characterize, and manage individuals with newly diagnosed HIV. Adopting recency testing and other HIV-testing initiatives in epidemic surveillance could help inform targeted prevention measures.

Author Contributions

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HIV incidence and prevalence among adults aged 15-64 years in Rwanda: Results from the Rwanda Population-based HIV Impact Assessment (RPHIA) and District-level Modeling, 2019

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ABSTRACT

Objectives: The 2018–2019 Rwanda Population–based HIV Impact Assessment (RPHIA) was conducted to measure national HIV incidence and prevalence. District-level estimates were modeled to inform resources allocation.

Methods: RPHIA was a nationally representative cross-sectional household survey. Consenting adults were interviewed and tested for HIV using the national diagnostic algorithm followed by laboratory-based confirmation of HIV status and testing for viral load (VL), limiting antigen (LAg) avidity, and presence of antiretrovirals. Incidence was calculated using normalized optical density ≤ 1·5, VL ≥ 1,000 copies/mL, and undetectable antiretrovirals. Survey and programmatic data were used to model district-level HIV incidence and prevalence.

Results: Of 31,028 eligible adults, 98·7% participated in RPHIA and 934 tested HIV positive. HIV prevalence among adults in Rwanda was 3·0% (95% CI:2·7–3·3). National HIV incidence was 0·08% (95% CI:0·02–0·14) and 0·11% (95% CI:0·00–0·26) in the City of Kigali (CoK). Based on district-level modeling, HIV incidence was greatest in the 3 CoK districts (0·11% to 0·15%) and varied across other districts (0·03% to 0·10%).

Conclusions: HIV prevalence among adults in Rwanda is 3.0%; HIV incidence is low at 0.08%. District-level modeling has identified disproportionately affected urban hotspots: areas to focus resources.

Introduction

Over the last decade, Rwanda's national HIV program has made tremendous achievements in accelerated scale-up of HIV testing, immediate linkage to antiretroviral treatment (ART) for those testing positive (test and treat), and other evidence-based prevention and treatment interventions such as condom availability, targeted HIV testing and index testing, scale up of prevention of mother to child transmission interventions, voluntary medical male circumcision (VMMC), and mass community education with specific focus towards key populations (Rwanda Ministry of Health, 2016, 2018). Collectively, these interventions have resulted in increased ART coverage, (Rwanda Ministry of Health, 2016, 2018, 2020) a decreased proportion of people living with HIV (PLHIV) with unsuppressed viral loads, stable/declining HIV prevalence, and

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progress towards the Joint United Nations Programme on HIV/AIDS (UNAIDS) 90–90–90 targets (Rwanda Ministry of Health, 2020; National Statistics of Rwanda, 2016; Nsanzimana et al., 2017a).

To measure the current status of the HIV epidemic and the progress of Rwanda's national HIV response, the Rwanda Population–based HIV Impact Assessment (RPHIA) was conducted in 2018–2019. RPHIA was designed to measure national and City of Kigali (CoK)–specific HIV incidence, national and provincial HIV viral load (VL) suppression, and HIV prevalence. However, RPHIA was not designed to provide HIV incidence, prevalence, and treatment coverage at a district level, which is crucial to better understand localized epidemics and guide the allocation of resources at the district level. To estimate HIV prevalence and incidence at the district level, we used the recently developed UNAIDS Naomi model, which allowed RPHIA data to be incorporated along with routinely collected programmatic data on ART coverage and antenatal HIV testing (UNAIDS, 2021; Eaton et al., 2021).

Here we present sex-specific national, provincial, and district-level estimates of HIV incidence and prevalence in adults aged 15–64 years in Rwanda.

Methods

RPHIA survey methods, sample size, and survey procedures are explained in the survey report.[3] Briefly, RPHIA was a nationally representative, cross-sectional population–based survey of households (HHs) across all 5 provinces in Rwanda. The survey used a 2-stage, stratified cluster sample design involving 375 enumeration areas (EAs) stratified by province using a probability proportional to size sampling approach. Within the sampled EAs, an average of 30 HHs (ranging from 14–60) were randomly selected. Individuals aged 10–64 years who slept in the sampled HH the night before (usual HH members or visitors) were eligible to participate in the survey. The analysis presented here is limited to participants aged 15–64 years.

Participants aged 18–64 years provided written informed consent. Parental or guardian permission and participant assent were required for persons aged 15–17 years. Completed HH and individual questionnaires and field laboratory data were transmitted electronically to a secure cloud server. Laboratory data were cleaned and merged with the final questionnaire data using unique study identification numbers. Anonymized data were used for statistical analyses. Sampling weights were computed to adjust for probability of selection, nonresponse, and noncoverage as previously described (Ministry of Health, 2020).

Laboratory Methods

Consenting participants provided venous blood for household-based HIV testing using the national guidelines, which included 2 tests: the Alere Combo (Alere Determine™ HIV-1/2 Ag/Ab Combo) (Alere Inc., Waltham, Massachusetts, United States) followed by the HIV 1/2 Stat-Pak™ (Chembio Diagnostic Systems, Medford, New York, United States). Blood specimens with a nonreactive result on the first test were classified as HIV negative. Those with a reactive result on both tests were classified as HIV positive. Specimens with a reactive first test result followed by a nonreactive second test result were classified as inconclusive and were excluded from the analysis. Home-based HIV test results were provided to the participants with appropriate counseling and referral to HIV testing and treatment services. All specimens that tested HIV positive during home-based testing were confirmed using the Geenius™ HIV 1/2 Supplemental Assay (Bio-Rad, Hercules, California, United States). A positive Geenius result defined HIV-positive status for the survey.

Plasma or dried blood spots (DBS) samples from individuals with confirmed HIV-positive status were tested to measure VL (HIV RNA copies/mL), using COBAS® TaqMan® Analyser on the COBAS AmpliPrep/COBAS TaqMan HIV-1 Test, v2.0 instrument (Roche Molecular Diagnostics, South Branchburg, New Jersey, United States) for plasma samples. The COBAS AmpliPrep/COBAS TaqMan HIV-1 Test v2.0 free virus elution protocol was used to measure VL from DBS specimens when plasma was insufficient.

Qualitative screening for detectable concentrations of the antiretrovirals (ARVs) efavirenz, tenofovir, nevirapine, and atazanavir was conducted at the University of Cape Town on DBS specimens from HIV-positive participants using high–resolution liquid chromatography coupled with tandem mass spectrometry (Rwanda Ministry of health, 2020). The ARVs were selected based on a review of routine program data on first and second-line ART regimens from a 3-month period before the end of the RPHIA data collection.

A recent infection testing algorithm was used to identify participants with a recent HIV infection. Samples from all confirmed HIV-positive participants were tested using the Maxim HIV-1 Limiting Antigen-Avidity (LAg) enzyme immunoassay (EIA) kit (Maxim Biomedical, Bethesda, Maryland, United States) on DBS and the HIV-1 LAg-Avidity EIA (Sedia Biosciences Corporation, Portland, Oregon, United States) on plasma. Specimens with median normalized optical density (ODn) $\leq$ 1·5 using plasma or ODn $\leq$ 1·0 when using DBS, VL $\geq$ 1,000 copies/mL, and no detectable ARVs were classified as cases of recent HIV infection.

Estimating incidence

Incidence estimates were based on the number of HIV infections identified by the recent infection testing algorithm and obtained using the formula recommended by the WHO Incidence Working Group and Consortium for Evaluation and Performance of Incidence Assays. Assay performance characteristics of a mean duration of recent infection = 130 days (95% CI 118, 142), a time cutoff = 1.0 year, and a percentage false recent = 0.00 were used in the incidence calculation (Rwanda Ministry of Health, 2020).

While RPHIA measured HIV incidence at the national level and in the CoK, too few recent HIV infections were observed in any district to derive a robust estimate of incidence. Therefore, to estimate HIV incidence at the district level, we used the Naomi model (UNAIDS, 2021).

Naomi is a Bayesian small-area estimation model intended for the estimation of HIV prevalence, number of PLHIV, ART coverage, and new HIV infections at the district level by sex and 5-year age groups.

The statistical model incorporated district-level data from the following sources: (1) the RPHIA HH survey data on HIV prevalence and ART coverage (based on self-reported and ARV detection data); (2) routine program data about the number receiving ART; (3) the HIV prevalence and ART coverage among pregnant women attending their first antenatal care (ANC) visit (both derived from the national HIV program indicator data reported from health facilities into the nationwide Rwanda Health Management Information System [RHMIS]); and (4) district population estimates from the 2012 census conducted by the National Institute of Statistics of Rwanda. RPHIA survey clusters were assigned to districts based on geo–masked cluster centroid locations and aggregated by district, sex, and 5-year age group using normalized sample weights. The model produced estimates at 3 time points: the year of the RPHIA survey in late 2018, the current period at which the most recent ART and ANC program data are available, and short-term 1-year ahead projections for HIV program planning purposes (UNAIDS, 2021).

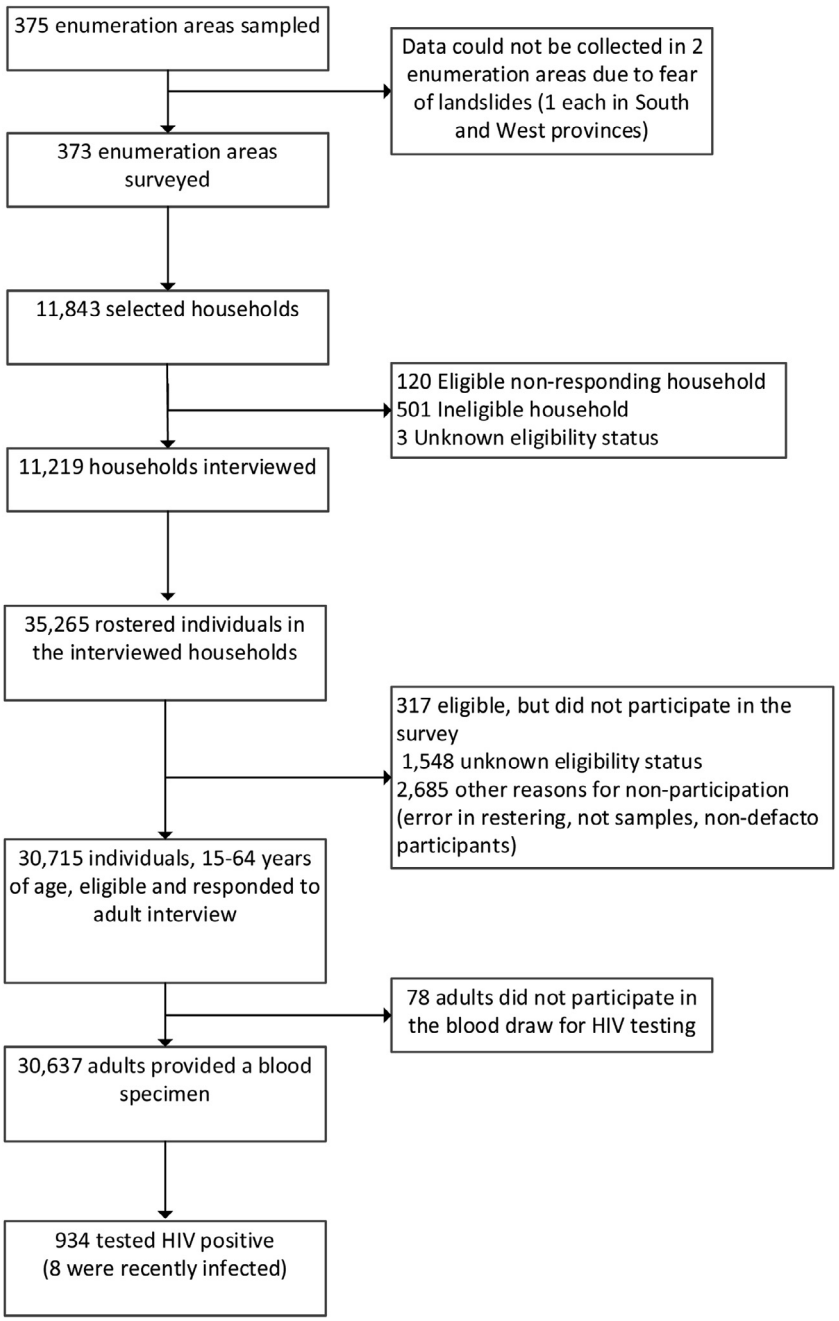

Figure 1. Participant flowchart in the Rwanda Population-based HIV Impact Assessment (RPHIA) 2018–2019

Analyses using RPHIA data alone

Two outcome variables were used in our analysis: confirmed HIV-positive status (based on Geenius confirmatory testing) was used to estimate HIV prevalence, and recent HIV infection status (defined by the recent infection testing algorithm described earlier) was used to estimate HIV incidence.

Sex-specific HIV incidence was calculated at the national and provincial level, by urban/rural residence, and by age. Sex-specific HIV prevalence estimates, disaggregated by sociodemographic characteristics, and sexual behaviors were computed. All results are weighted, unless otherwise noted, to account for sample selection probabilities and adjusted for nonresponse and noncoverage (Rwanda Ministry of Health, 2020). Post-stratification to compensate for noncoverage in the sampling process was done by adjusting the weights so that the sum of each set of weights conformed to national population totals by sex and 5-year age groups from the 2018 national population projections from the 2012 national census. Finally, interview and blood weight normalization factors were applied so that the final sum of weights matched the number of respondents to the interview and blood draw, respectively. Variance was estimated using jackknife replicate weights (RPHIA 2018-2019 Sampling and Weighting Technical Report, 2019). All extrapolations made to the population are based on survey weighting. The data were analyzed using SAS 9.4 1 (SAS Institute Inc., Cary, North Carolina, United States).

To transition from the RPHIA-specific analysis of HIV prevalence at the national and provincial level to the district-level estimates from Naomi, the Naomi-derived HIV prevalence estimates and quantile-based 95% Credible Interval at the provincial level

Table 1
Prevalence of HIV among persons aged 15–64 years, by sex and selected demographic, sexual behaviour characteristics, RPHIA, 2018–2019.

	Male		Female		Total	
Characteristic	%HIV positive	N	%HIV positive	N	%HIV positive	N
Age						
15–19	0.4 (0.2–0.6)	3,071	0.8 (0.4–1.1)	3,347	0.6 (0.4–0.8)	6,418
20–24	0.6 (0.2–0.9)	2,217	1.8 (1.2–2.4)	2,723	1.2 (0.9–1.5)	4,940
25–29	1.3 (0.6–1.9)	1,869	3.4 (2.5–4.3)	2,394	2.4 (1.8–2.9)	4,263
30–34	1.4 (0.8–2.0)	1,777	3.7 (2.7–4.7)	2,120	2.6 (1.9–3.2)	3,897
35–39	2.9 (2.1–3.8)	1,567	4.5 (3.4–5.6)	1,770	3.7 (3.0–4.5)	3,337
40–44	4.9 (3.4–6.4)	950	7.1 (5.6–8.6)	1,342	6.1 (4.9–7.3)	2,292
45–49	5.6 (3.9–7.4)	716	7.0 (5.3–8.8)	963	6.4 (5.0–7.8)	1,679
50–54	6.3 (4.2–8.4)	594	7.4 (5.6–9.2)	812	6.9 (5.5–8.3)	1,406
55–59	6.5 (4.1–9.0)	516	5.9 (3.8–7.9)	728	6.2 (4.5–7.8)	1,244
60–64	3.3 (1.7–4.9)	503	4.4 (2.7–6.1)	658	3.9 (2.7–5.2)	1,161
Residence						
Urban	3.2 (2.4–3.9)	3,570	6.5 (5.3–7.7)	4,061	4.8 (4.0–5.7)	7,631
Rural	2.0 (1.6–2.3)	10,210	3.0 (2.7–3.4)	12,796	2.5 (2.2–2.8)	23,006
Province						
City of Kigali	3.0 (2.4–3.7)	2,752	5.7 (4.5–6.9)	2,982	4.3 (3.5–5.1)	5,734
Urban	3.1 (2.4–3.8)	2,304	5.7 (4.4–7.0)	2,472	4.3 (3.5–5.1)	4,776
Rural	2.8 (1.1–4.5)	448	5.4 (2.3–8.4)	510	4.1 (2.0–6.1)	958
South	2.3 (1.5–3.1)	2,712	3.4 (2.6–4.2)	3,414	2.9 (2.2–3.6)	6,126
Urban	3.6 (0.9–6.4)	340	5.5 (4.1–7.1)	408	4.6 (2.7–6.6)	748
Rural	2.1 (1.5–2.7)	2,372	3.1 (2.3–4.0)	3,006	2.6 (2.0–3.3)	5,378
West	2.4 (1.6–3.2)	3,225	3.6 (2.6–4.6)	4,251	3.0 (2.2–3.9)	7,476
Urban	3.7 (1.7–5.7)	461	7.4 (3.8–11.1)	637	5.8 (3.2–8.4)	1,098
Rural	2.2 (1.4–3.0)	2,764	2.9 (2.2–3.5)	3,614	2.5 (1.9–3.2)	6,378
North	1.5 (1.2–1.9)	2,586	2.8 (2.2–3.3)	3,323	2.2 (1.8–2.6)	5,909
Urban	1.0 (0.0–2.0)	271	6.0 (3.8–8.3)	317	3.5 (1.6–5.4)	588
Rural	1.6 (1.2–2.0)	2,315	2.4 (1.9–2.9)	3,006	2.0 (1.6–2.4)	5,321
East	2.0 (1.3–2.7)	2,505	3.9 (2.9–4.9)	2,887	2.9 (2.2–3.7)	5,392
Urban	3.9 (1.2–6.6)	194	10.2 (6.4–14.0)	227	7.0 (4.3–9.8)	421
Rural	1.8 (1.2–2.4)	2,311	3.3 (2.5–4.1)	2,660	2.6 (1.9–3.2)	4,971
Marital status						
Never married	0.9 (0.6–1.2)	6,610	2.0 (1.6–2.3)	6,349	1.4 (1.1–1.6)	12,959
Married or living together	3.0 (2.5–3.5)	6,740	3.0 (2.5–3.5)	8,008	3.0 (2.6–3.6)	14,748
Divorced or separated	7.5 (4.7–10.3)	351	8.0 (6.1–9.9)	1,328	7.9 (6.3–9.5)	1,679
Widowed	10.8 (3.3–18.3)	73	12.0 (9.9–14.1)	1,162	11.9 (9.9–14.0)	1,235
Education						
No education	4.3 (2.9–5.8)	1,004	6.0 (4.8–7.3)	1,865	5.4 (4.4–6.4)	2,869
Primary	2.3 (1.9–2.7)	8,431	3.9 (3.4–4.5)	9,931	3.2 (2.7–3.6)	18,362
Secondary	1.5 (1.0–1.9)	3,558	2.3 (1.8–2.8)	4,397	1.9 (1.5–2.2)	7,955
More than secondary	1.1 (0.3–1.9)	782	2.2 (0.7–3.6)	648	1.5 (0.7–2.4)	1,430
Wealth quintile						
Lowest	2.2 (1.5–3.0)	2,166	3.1 (2.4–3.9)	3,123	2.7 (2.1–3.4)	5,289
Second	1.6 (1.1–2.1)	2,396	2.8 (2.1–3.5)	3,166	2.3 (1.8–2.7)	5,562
Middle	2.3 (1.6–2.9)	2,635	3.2 (2.6–3.8)	3,169	2.8 (2.2.3.3)	5,804
Fourth	2.4 (1.8–3.0)	2,864	4.7 (3.8–5.6)	3,230	3.6 (2.9–4.2)	6,094
Highest	2.5 (1.9–3.1)	3,707	4.7 (3.7–5.6)	4,162	3.6 (2.9–4.2)	7,869
Pregnancy status						
Currently pregnant	NA	NA	2.3 (1.3–3.2)	979	NA	NA
Not currently pregnant	NA	NA	3.8 (3.4–4.3)	15,729	NA	NA
Age at first sexual intercourse						
<15	1.7 (0.8–2.6)	980	5.8 (3.8–7.9)	563	3.1 (2.1–4.1)	1,543
15–19	2.9 (2.3–3.5)	3,708	5.9 (5.0–6.8)	5,922	4.7 (4.0–5.3)	9,630
20–24	2.9 (2.3–3.5)	3,552	3.2 (2.7–3.8)	4,801	3.1 (2.6–3.5)	8,353
≥25	2.6 (1.8–3.4)	2,081	3.5 (2.4–4.5)	1,625	3.0 (2.3–3.6)	3,706
Number of sexual partners in the past 12 months						
0	2.4 (1.6–3.2)	1,611	7.2 (6.2–8.3)	3,007	5.4 (4.7–6.2)	4,618
1	2.6 (2.1–3.0)	6,944	3.2 (2.7–3.7)	9,313	2.9 (2.5–3.3)	16,257
≥2	3.8 (2.8–4.8)	1,809	13.0 (9.8–16.1)	631	5.9 (4.7–7.0)	2,440
Condom use at last sexual intercourse in the past 12 months						
Used condom	6.5 (5.0–7.9)	1,446	10.5 (8.2–12.7)	1,103	8.1 (6.7–9.4)	2,549
Did not use condom	2.0 (1.6–2.4)	6,599	2.6 (2.2–3.1)	8,562	2.3 (1.9–2.7)	15,161
No sexual intercourse in the past 12 months	2.4 (1.6–3.2)	1,611	7.2 (6.2–8.3)	3,007	5.4 (4.7–6.2)	4,618
Total 15–24	0.5 (0.3–0.7)	5,288	1.2 (0.9–1.5)	6,070	0.9 (0.7–1.1)	11,358
Total 15–49	1.8 (1.5–2.1)	12,167	3.3 (2.9–3.8)	14,659	2.6 (2.3–2.9)	26,826
Total 15–64	2.2 (1.9–2.6)	13,780	3.7 (3.3–4.1)	16,857	3.0 (2.7–3.3)	30,637

NOTES:
(1) Weighted figures calculated using final blood test weights.
(2) The sum of the sample sizes for a given classification may be less than the total sample size because of missing responses to the classification variable.

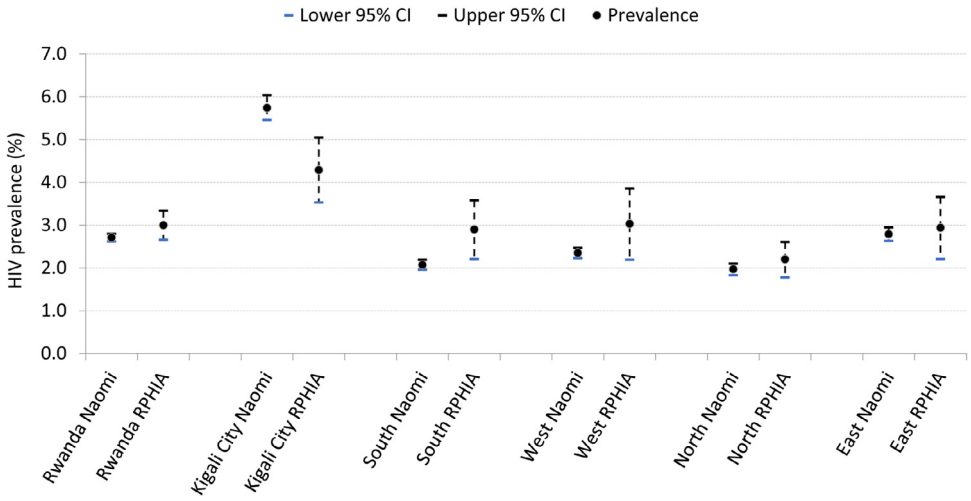

Figure 2. HIV prevalence in Rwanda measured in RPHIA and the estimate from Naomi model, at the national and provincial level, 2018–2019.
Footnote: The error bars represent RPHIA 95% confidence intervals for the RPHIA estimates and quantile-based 95% credible intervals for the Naomi estimates

have been presented alongside the RPHIA results (HIV prevalence and 95% Confidence Interval), followed by the district-level estimates of prevalence and incidence from the UNAIDS Naomi model stratified by sex (Eaton et al., 2021).

Lastly, a correlation between HIV prevalence and incidence at the district level was estimated, overall (both sexes) and by sex, to assess the relationship between prevalence and incidence at a granular (district) level in Rwanda. We fit a linear model between incidence and prevalence to measure the slope of a linear fit for incidence as a function of HIV prevalence.

Results

In the 11,219 households which were sampled and responded to the household interview, 35,265 individuals were rostered, 30,715 were eligible for RPHIA participation, and 30,637 provided a blood sample for HIV and other biomarker testing. Of the 30,637 tested for HIV, 934 were confirmed to be HIV positive. (Figure 1).

HIV prevalence

Overall HIV prevalence was 3·0% (95% CI 2·7–3·3) among adults aged 15–64 years and 2·6% (95% CI 2·3–2·9) among adults aged 15–49 years (Table 1). HIV prevalence was highest among men aged 55–59 years (6·5%; 95% CI 4·1–9·0) and women aged 50–54 years (7·4%; 95% CI 5·6–9·2). National HIV prevalence was significantly higher among women than men (3·7%; 95% CI 3·3–4·1 versus 2·2; 95% CI 1·9–2·6) and a similar pattern was observed in every province. The sex disparity in HIV prevalence was greatest among the young adults aged 20–24 years, with HIV prevalence in women 3-times higher than in men. HIV prevalence varied by province, ranging from 2·2% (95% CI 1·8–2·6) in the north to 4·3% (95% CI 3·5–5·1) in the predominantly urban CoK. At the national level, urban areas had higher HIV prevalence (4·8%; 95% CI 4·0–5·7) than rural areas (2·5%; 95% CI 2·2–2·8), and within each province, urban areas had higher HIV prevalence than rural areas. HIV prevalence was lowest among those who had attained higher education, but it did not differ by wealth quintile. Women who reported first sexual intercourse at age <15 years were 3 times more likely to be HIV positive than men who reported first sexual intercourse at age <15 years. HIV prevalence did not differ by the number of sexual partners among men; among women, however, those who reported having more than 2 partners in the last 12 months had a higher HIV prevalence (13·0%) than those who reported having had 1 partner in the past 12 months (3·2%). HIV prevalence was higher among those who reported having used condoms at last sexual intercourse (8·1% (95% CI 6·7–9·4) than those who reported not having used condoms at the last sexual intercourse (2·3%; 95% CI 1·9–2·7); this difference was much larger among women than men.

Applying the HIV prevalence measured in RPHIA to the 2018 population projection of people aged 15–64 years based on the 2012 national census, we estimated the number of PLHIV aged 15–64 years in 2018 in Rwanda to be 210,200 (95% CI 186,400–234,000). Distribution of PLHIV in Rwanda by age group was as follows: 20,800 (95% CI 16,100–25,600) in the 15–24 year age-band; 48,100 (95% CI 39,200–57,000) in the 25–34 year age-band; and 88,700 (95% CI 75,700–101,700) in the 35–49 year age-band (not shown in table).

HIV prevalence estimates from RPHIA and the Naomi model at the provincial level are shown in Figure 2.

District-level HIV prevalence estimates from the Naomi model were greatest among the 3 districts of the CoK, ranging from 5·1% (95% CI 4·5–5·7) in Gasabo to 7·2% (95% CI 6·1–8·3) in Nyarugenge. There was substantial variation in HIV prevalence across districts, ranging from 1·2% (95% CI 1·0–1·4) in Nyaruguru in the southern province to 7·2% (95% CI 6·1–8·3) in Nyarugenge in the CoK (Figure 3; Supplemental Table 1).

HIV Incidence

Eight of the 934 HIV-positive participants in RPHIA were classified as having a recent HIV infection based on the recent infection testing algorithm. Based on these 8 cases, the annual incidence of HIV infection among adults 15–64 years was estimated as 0·08% (95% CI 0·02–0·14) in Rwanda and 0·11% (95% CI 0·00%–0·26%) in the CoK. HIV incidence was 0·09% (95% CI 0·00–0·17) among men and 0·07% (95% CI 0·00–0·15) among women; 0·12% (95% CI 0·00–0·27) in urban areas, and 0·07% (95% CI 0·01–0·13) in rural areas (Table 2).

Based on these incidence estimates, the extrapolated number of new HIV infections in Rwanda in 2018–2019 was 5,400 (95% CI 1,400–9,400).

Based on UNAIDS Naomi district-level modeling, HIV incidence was highest in the 3 districts that make up the CoK–0·11% (95% CI 0·09–0·12) in Gasabo, 0·12% (95% CI 0·10–0·14) in Kicukiro, and 0·15% (95% CI 0·13–0·18) in Nyarugenge. HIV incidence varied across the 30 districts of Rwanda; outside of the CoK, HIV incidence ranged from 0·03% (95% CI 0·02–0·04) in Burera to

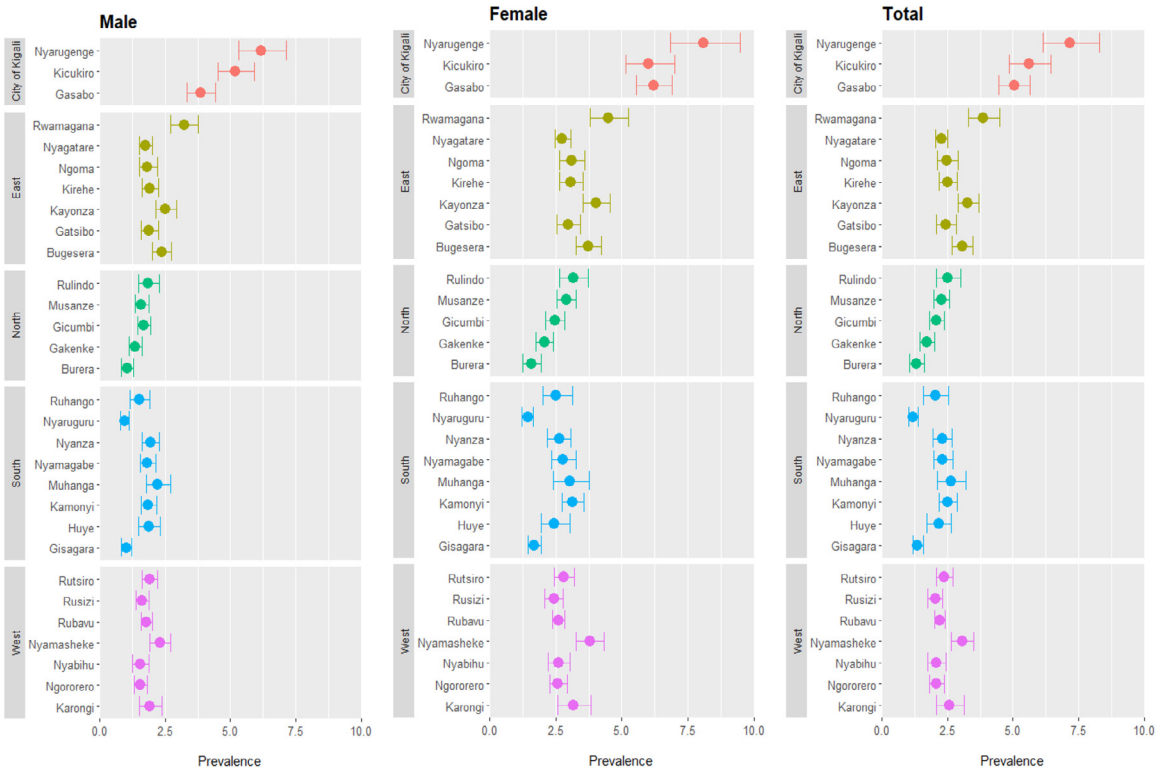

Figure 3. Naomi model–based estimates of HIV prevalence and 95% credible intervals by district and gender among adults aged 15–64 years, 2018–19.
Footnote: The solid dots represent the point estimates and the error bars represent the quantile-based 95% credible intervals derived from the Naomi model.

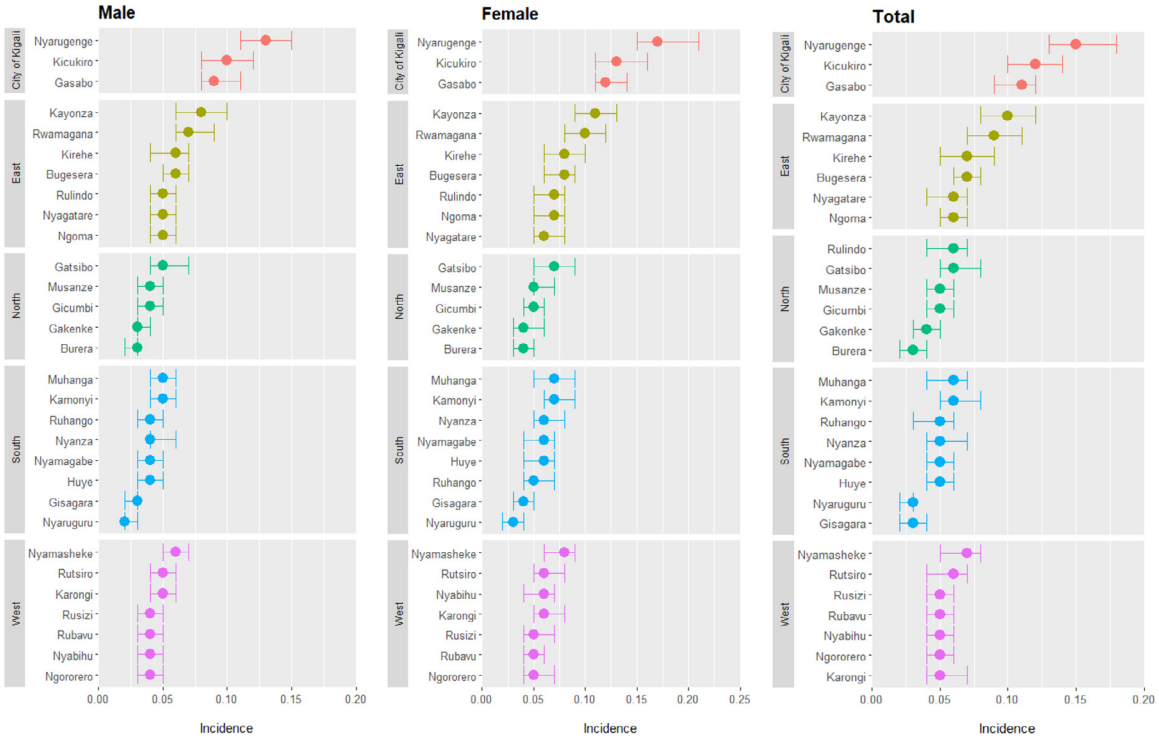

Figure 4. Naomi model–based estimates of HIV incidence and 95% credible intervals by district and gender among adults aged 15–64 years, 2018–19.
Footnote: The solid dots represent the point estimates and the error bars represent the quantile-based 95% credible intervals derived from the Naomi model.

Table 2
Annual HIV incidence by residence, province, age, and sex, using the recent infection testing algorithm (using limiting antigen [Lag], viral load [VL], and antiretroviral [ARV] biomarker), RPHIA, 2018–2019.

Characteristic	Number of estimated HIV positive and HIV recent infections									Annual HIV incidence					
	Male			Female			Total			Male		Female		Total	
	No. of HIV -ve[1] (N)	No. of HIV +ve (P) tested on LAg assay[1] (Q)	No. of HIV recent[1] (R)	Number HIV -ve[1] (N)	No. of HIV +ve (P) tested onLAg assay[1](Q)	Number HIV recent[1] (R)	No. of HIV -ve[1] (N)	No. of HIV +ve (P) tested onLAg assay[1](Q)	No. of HIV recent[1] (R)	Percentage annual incidence[1]	95% CI	Percentage annual incidence[1]	95% CI	Percentage annual incidence[1]	95% CI
sidence[2]															
ban	3456.7	113.3	0.8	3796.4	264.6	2.4	7261.7	369.3	3.1	0.07	0.00–0.21	0.18	0.00–0.46	0.12	0.00–0.27
ral	10008.8	201.2	3.3	12408.3	387.7	2.2	22424.4	581.6	5.5	0.09	0.00–0.20	0.05	0.00–0.12	0.07	0.01–0.13
ovince[2]															
ty of Kigali	2668.9	83.1	1.1	2812.8	169.2	1.1	5488.0	246.0	2.2	0.11	0.00–0.33	0.11	0.00–0.32	0.11	0.00–0.26
uth	2649.8	62.2	0.0	3296.8	117.2	2.0	5948.5	177.5	1.9	0.00	0.00–0.39	0.17	0.00–0.42	0.09	0.00–0.22
est	3147.9	77.1	2.0	4099.3	151.7	1.0	7249.8	226.2	3.1	0.17	0.00–0.42	0.07	0.00–0.21	0.12	0.00–0.25
rth	2545.9	40.1	0.0	3231.2	91.8	0.0	5779.2	129.8	0.0	0.00	0.00–0.41	0.00	0.00–0.32	0.00	0.00–0.18
st	2455.4	49.6	1.1	2775.1	111.9	0.0	5233.6	158.4	1.2	0.13	0.00–0.37	0.00	0.00–0.37	0.06	0.00–0.19
ge															
–24	5263.1	24.9	0.9	5994.7	75.3	1.3	11260.1	97.9	2.2	0.05	0.00–0.15	0.06	0.00–0.20	0.06	0.00–0.14
25–34	3597.2	48.8	3.1	4355.0	159.0	0.7	7959.3	200.7	4.0	0.24	0.00–0.51	0.04	0.00–0.14	0.14	0.00–0.28
35–49	3098.8	134.2	0.0	3832.6	242.4	1.0	6935.2	372.8	1.0	0.00	0.00–0.33	0.08	0.00–0.22	0.04	0.00–0.12
15–49	11952.0	215.0	4.2	14169.1	489.9	3.0	26134.1	691.9	7.3	0.10	0.00–0.20	0.06	0.00–0.13	0.08	0.02–0.14
15–64	13473.2	306.8	4.1	16232.0	625.0	4.3	29718.6	918.4	8.4	0.09	0.00–0.17	0.07	0.00–0.15	0.08	0.02–0.14

[1] Weighted number
[2] Residence figures are among adults aged 15–64 years.
Note: mean duration recent infection = 130 days (95% CI 118–142 days); proportion false recent = 0.00; time cutoff = 1 year
RPHIA was designed to estimate incidence of HIV at the national level and in the City of Kigali.
Although incidence was estimated for the other provinces, these estimates should be interpreted with caution.

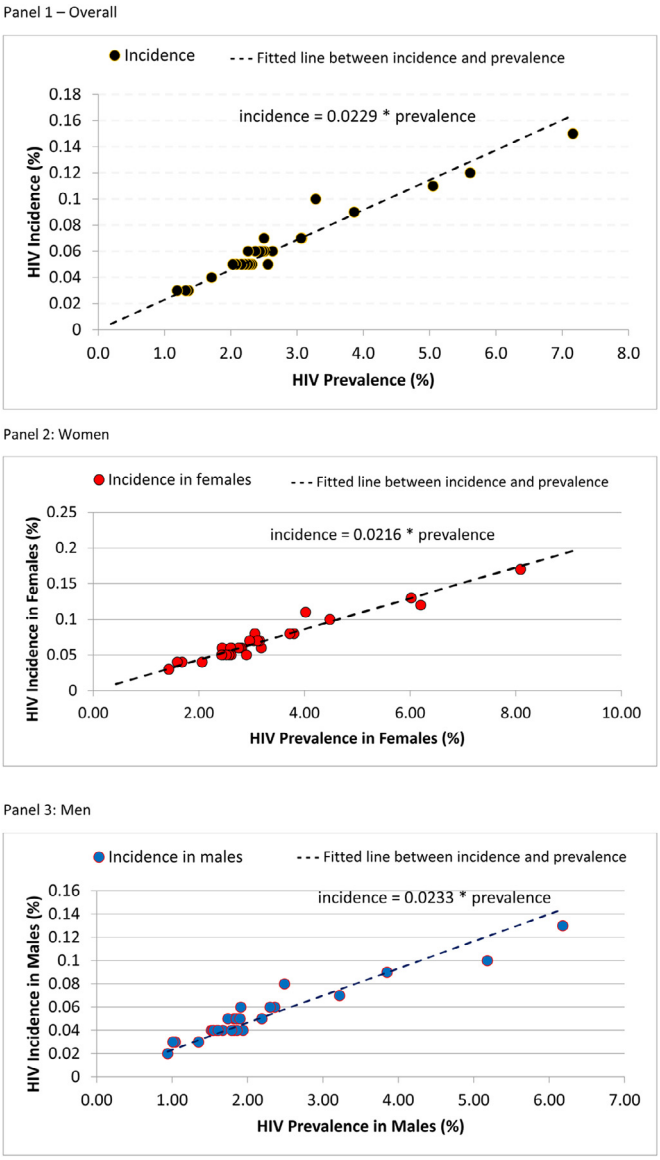

Figure 5. Correlation between HIV incidence and prevalence at the district level, overall (Panel 1) and by gender (Panel 2 shows women and Panel 3 shows men), among adults aged 15–64 years old in Rwanda, 2018–2019
Panel 1 – Overall
Panel 2: Women
Panel 3: Men
Note that HIV incidence and prevalence at the district level were estimated from the Naomi model.

0·10% (95% CI 0·08–0·12) in Kayonza in the eastern province (Figure 4).

Correlation between HIV incidence and prevalence at a district level

Plotting district-level HIV incidence and prevalence, overall and by sex, using the UNAIDS Naomi model shows a strong correlation between these 2 measures (Figure 5). Using our findings, we can estimate incidence in females using the equation y = 0.0216 * prevalence (females) and in males using the equation y = 0.0233 * prevalence (males).

Discussion

We described Rwanda's national HIV prevalence and incidence using empirical data from RPHIA conducted in 2018–2019. HIV incidence in RPHIA, using the recent infection testing detection algorithm, was lower than the previous estimate in 2015 of 0·27% (95% CI 0·13–0·35) (Nsanzimana et al., 2017a; Rwanda Ministry of Health 2020). We also reported on the district-level HIV incidence and prevalence estimates using the Naomi small area estimates model which provides granular level evidence of the status of the epidemic for program planning and resource allocation.

Through the nationally representative RPHIA survey conducted from 2018–2019, a national HIV incidence of 0·08% was estimated in Rwanda. The last empirical measurement of HIV incidence in Rwanda was through the Rwanda AIDS Indicator and HIV Incidence Survey in 2014–2015, which used a prospective cohort design of following up HIV-negative individuals and retesting them after a year of follow-up (Nsanzimana et al., 2017a). This study measured HIV incidence of 0·27% (95% CI 0·13–0·35) but used a different study design and HIV testing methods. The 2019 HIV incidence calculated through the UNAIDS Spectrum model was 0·06% which takes into account HIV program data, demographic information, and other surveillance and survey data. Taken together, HIV incidence in Rwanda is low, but subnational analyses using RPHIA together with other programmatic data have identified areas of higher incidence which are otherwise masked by the national average.

HIV prevalence in Rwanda has stabilized at 3·0% over the last 15 years from 3·0% in 2005, 2010, and 2014–2015 measured in the Rwanda Demographic Health Survey (RDHS) and Rwanda AIDS Indicator and HIV Incidence Survey to 2·6% measured in RPHIA 2018–2019 (National Institute of Statistics Rwanda, 2006, 2012, 2016; Nsanzimana et al., 2017a). HIV prevalence among those aged 15–64 years remained at 3·0%. The shift in HIV prevalence may reflect the cohort effect of aging PLHIV, especially as the peak age of HIV prevalence has been shifting to the older age groups over time and is consistent with declining mortality among PLHIV due to "Treat All" with high coverage of ART and a declining HIV incidence in Rwanda (Nsanzimana et al., 2017a, 2017b; Binagwaho et al., 2014, Nash et al., 2018).

A key finding from RPHIA was the high HIV prevalence seen in urban areas in provinces outside of the CoK, an observation made by other studies in sub–Saharan Africa (Borgdorff et al., 2018; Vandormael et al., 2019; Lesotho, 2019). Compared with rural areas, urban areas in Rwanda have a larger population size of female sex workers, men who have sex with men, and persons who inject drugs (Ingabire et al., 2019; Mutagoma et al., 2015). The point estimates for HIV prevalence in the CoK have decreased from 6·3% to 3·7% in the last 5 years for those aged 15–49 years (Nsanzimana et al., 2017a; Rwanda Ministry of Health 2020). This decline in prevalence in the CoK may be attributed to the reduced number of new infections due to increased ART coverage, substantial numbers of PLHIV aging from the 15–49 age group to the 50+ age group, and population increase in the CoK with more HIV-negative male youths coming from the villages to look for work. It is important to note that there may be methodologic differences that may contribute to these observed differences between the RDHS and RPHIA estimates; DHS did not stratify by age and sex and young men are less likely to participate in a HH survey. Of note, this decrease in HIV prevalence may also be related to the expansion of the CoK boundaries to include more rural areas in the last 5–10 years.

In our study, HIV prevalence was higher among those who reported having used condoms in the last sexual intercourse. Among PLHIV in Rwanda, 83·8% are aware of their HIV-positive status (Rwanda Ministry of Health, 2020), and receive counseling and access to condoms, which might contribute to high condom usage among those who are HIV-positive (Rwanda Ministry of Health, 2016, 2018, 2020). Similar findings were reported in a study in South Africa where men and women who reported condom use at last sexual intercourse were at increased risk of HIV, ei-

ther due to inconsistent use of condoms or due to social desirability bias in self-reporting condom use (Mabaso et al., 2019). U=U policy was launched in Rwanda in October 2021 and will guide HIV prevention interventions going forward (KT Press, 2021).

District-level modeling for HIV prevalence and incidence has provided a better understanding of the micro-level epidemics in Rwanda. The use of population-based survey data along with other programmatic data provided district-level estimates with greater precision which could not be obtained through RPHIA alone. These modeled estimates have helped identify districts outside of CoK as areas of high incidence and help with resource allocation and planning of interventions. However, further interrogation of the data inputs into Naomi is required.

Data to estimate HIV incidence at the district level are very sparse, and so the district incidence estimates are required to make many assumptions, for example, the sex ratio and age pattern of incidence are assumed to be the same across all districts. We also show that using HIV prevalence and incidence from the Naomi model, we can construct an equation that can be used to determine the incidence of subnational populations given known HIV prevalence for that population and geography. Measuring incidence at small geographical areas is expensive and this correlation between prevalence and incidence would help obtain estimates of incidence without undertaking direct measurements of the same.

Conclusion

HIV prevalence in Rwanda has stabilized at 3·0% over the last 15 years; RPHIA demonstrated a prevalence of 2·6% among those aged 15–49 years and a maintenance of prevalence at 3·0% among those aged 15–64 years, indicating a cohort effect of aging PLHIV. Urban settings other than the CoK have been disproportionately affected and interventions addressing prevention, care, and treatment, and retention in care need to be adapted in these smaller geographies in light of RPHIA and district-level findings. Maintaining the gains made by the national HIV response is critical. Findings from this study will help the national HIV program in Rwanda to streamline its future interventions and priorities to achieve sustained epidemic control.

Declaration of Competing Interest

The authors have no conflict of interest to declare.

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Ethical approval statement

Human subjects and ethical approval for the RPHIA survey was granted by the Rwanda National Ethics Committee (Ref: IRB-00001497) and the Institutional Review Boards of the United States Centers for Disease Control and Prevention ([CDC; Atlanta, Georgia, US] [Ref: #6760] and Columbia University Irving Medical Center [Ref. IRB-AAAR8357]).

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Disclaimer

The findings and conclusions in this manuscript are those of the authors and do not necessarily represent the official position of the funding agencies.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.01.032.

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