

RESEARCH ARTICLE

Cost-Effectiveness of the 'One4All' HIV Linkage Intervention in Guangxi Zhuang Autonomous Region, China

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Abstract

Background

In Guangxi Zhuang Autonomous Region, China, an estimated 80% of newly-identified anti-retroviral therapy (ART)-eligible patients are not engaged in ART. Delayed ART uptake ultimately translates into high rates of HIV morbidity, mortality, and transmission. To enhance HIV testing receipt and subsequent treatment uptake in Guangxi, the Chinese Center for Disease Control and Prevention (CDC) executed a cluster-randomized trial to assess the effectiveness and cost-effectiveness of a streamlined HIV testing algorithm (the One4All intervention) in 12 county-level hospitals.

Objective

To determine the incremental cost-effectiveness of the One4All intervention delivered at county hospitals in Guangxi, China, compared to the current standard of care (SOC).

Perspective

Health System.

Time Horizon

1-, 5-and 25-years.

Methods

We adapted a dynamic, compartmental HIV transmission model to simulate HIV transmission and progression in Guangxi, China and identify the economic impact and health benefits of implementing the One4All intervention in all Guangxi hospitals. The One4All intervention algorithm entails rapid point-of-care HIV screening, CD4 and viral load testing of individuals presenting for HIV screening, with same-day results and linkage to

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counselling. We populated the model with data from the One4All trial (CTN-0056), China CDC HIV registry and published reports. Model outcomes were HIV incidence, mortality, costs, quality-adjusted life years (QALYs), and the incremental cost-effectiveness ratio (ICER) of the One4All intervention compared to SOC.

Results

The One4All testing intervention was more costly than SOC (CNY 2,182 vs. CNY 846), but facilitated earlier ART access, resulting in delayed disease progression and mortality. Over a 25-year time horizon, we estimated that introducing One4All in Guangxi would result in 802 averted HIV cases and 1629 averted deaths at an ICER of CNY 11,678 per QALY gained. Sensitivity analysis revealed that One4All remained cost-effective at even minimal levels of effectiveness. Results were robust to changes to a range of parameters characterizing the HIV epidemic over time.

Conclusions

The One4All HIV testing strategy was highly cost-effective by WHO standards, and should be prioritized for widespread implementation in Guangxi, China. Integrating the intervention within a broader combination prevention strategy would enhance the public health response to HIV/AIDS in Guangxi.

Introduction

Experimental and observational studies across diverse patient populations worldwide have confirmed the individual and public health benefits of antiretroviral therapy (ART) [1,2,3,4,5]. However, in many settings, including China, significant proportions of people living with HIV/AIDS (PLHIV) are lost at each step along the continuum of HIV care, a patient pathway which includes diagnosis, linkage to care, ART engagement, and ultimately viral suppression [6,7].

Strategies to seek, test, treat and retain PLHIV provide a process framework for engaging HIV-positive, treatment-eligible patients in ART with the ultimate goal of helping patients achieve and sustain viral suppression, thereby extending their lives and reducing onward HIV transmission. Engaging and retaining PLHIV in HIV care presents perhaps the greatest challenge to achieving international goals of reducing HIV morbidity, mortality and transmission [8].

In 2011, Guangxi Zhuang Autonomous Region, China, with 46.5 million population, had an estimated HIV prevalence of 80,000–100,000 (10% to 13% of the national total of 780,000) [9]. Only 40% of those who screened HIV-positive at hospital settings received confirmatory testing, and only 85% of those confirmed to be HIV-positive received their HIV test results, resulting in substantial cascade leakage at the point of diagnosis. Furthermore, 38% of PLHIV who were notified of their HIV-positive status failed to receive CD4 testing. As a result, nearly 80% of newly-identified, ART-eligible patients in Guangxi are not engaged in ART [10]. These missed opportunities for patient engagement in HIV care ultimately translate into high rates of developing AIDS and mortality. Guangxi had the highest newly-reported AIDS cases (7,571, 19% of the national total), and the highest number of AIDS-related deaths (3,852, 22% of the national total) among all provinces in China [11].

The CTN-0056 study was designed to address deficits in HIV diagnosis and linkage to care. The 'One4All' test intervention entailed a streamlined testing algorithm consisting of rapid point-of-care (POC) HIV testing, POC CD4 testing, and viral load (VL) testing with same-day results and linkage to post-CD4 counselling [12]. SOC, on the contrary, employed multistage stepwise procedures requiring initial screening testing, western blot confirmation testing, traditional CD4 testing and multiple counselling at discrete times prior to treatment initiation, resulting in significant disengagements along each step and typically a ≥ 15 days delay in initiating ART for those eligible. Piloted in 12 hospitals across Guangxi Zhuang Autonomous Region and implemented by the National Center for AIDS/STD Control and Prevention of the Chinese Center for Disease Control and Prevention (NCAIDS, China CDC), the trial was positioned for immediate scale-up across the region if deemed effective in increasing the adjusted odds of HIV test receipt and subsequent ART uptake among those eligible.

Prioritizing cost-effective interventions is central to developing an effective and sustainable public health strategy for HIV/AIDS. Although a wide variety of interventions have proven effective in improving HIV care along the continuum, and many more currently being tested in a wide range of settings [13], systematic reviews summarizing cost-effectiveness analysis for HIV care interventions noted large knowledge gaps in the literature, particularly on linkage interventions [14,15]. Moreover, many HIV care interventions are executed without formal economic evaluations [16,17,18]. Formal economic evaluation, built upon a dynamic transmission modeling framework, can provide credible evidence of the value of these interventions, thus establishing an evidence-based framework for priority setting and resource allocation.

Our objective was to determine the incremental cost-effectiveness of the One4all testing intervention compared to the current standard of care delivered in county hospitals in Guangxi Zhuang Autonomous Region, China. We populated a previously-validated dynamic HIV transmission model [19,20] with trial data and routinely collected treatment engagement and disease progression data for the region of Guangxi in order to determine the cost-effectiveness of the One4All intervention compared to the standard of care over a 25-year time horizon.

Methods

2.1 The CTN-0056 Trial

CTN-0056 was a cluster-randomized trial conducted simultaneously in 12 county general hospitals which recruited a total of 478 adults who actively sought for inpatient or outpatient care in selected hospitals and screened positive on an initial HIV enzyme immunoassay (EIA) between February 24, 2014 and November 25, 2014 and were followed for 12 months. Study hospitals were selected for homogeneity in structural characteristics, past patient caseloads, and testing procedures. Hospitals were randomized to (1) the One4All test intervention, or (2) the control condition, 6 in each arm, consisting of the current standard of care (SOC), resulting in 232 patients in One4All arm and 246 patients in the SOC arm. There were no significant differences between the arms in patient demographics except that the One4all arm had more participants who completed middle school or higher (40.1%) than SOC (22.8%; $p = 0.0498$). The trial received approval from the Institute Review Board of the NCAIDS, China CDC, and the University of California, Los Angeles Institutional Review Board. This trial is registered with ClinicalTrials.gov, with identifier number (NCT02084316).

The primary outcome of the trial was defined as the proportion of participants who achieved testing completeness and received their test results and post-test counseling within 30 days, given they have received a positive HIV result on the initial EIA screening. Testing completeness is defined as completion of three required components: (1) Initial EIA; (2) CD4 testing and (3) confirmatory testing—western blot in the SOC, or confirmatory VL in the

Table 1. Timing and components of the One4All Intervention and Standard of Care (SOC).

	Standard of Care (SOC)	One4All Intervention
Baseline	<ul style="list-style-type: none"> • 2 point-of-care HIV screening tests + counseling • Western blot confirmatory test blood draw 	<ul style="list-style-type: none"> • 2 point-of-care HIV screening tests + counseling • Point-of-care CD4 count blood draw • CD4 results + counseling • Viral load test blood draw
Follow-up 1 (10–15 days)	<ul style="list-style-type: none"> • Western blot results + counseling • CD4 count blood draw 	<ul style="list-style-type: none"> • Viral load results + counseling*
Follow-up 2 (10–15 days for SOC)	<ul style="list-style-type: none"> • CD4 results + counseling* 	<ul style="list-style-type: none"> • ART counseling + initiation
Follow-up 3	<ul style="list-style-type: none"> • ART counseling + initiation • Viral load test blood draw (after ART initiation) 	

*Indicates point of testing completeness

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One4all arm. The secondary outcome is the proportion of ART eligible participants who initiate ART within 90 days of their initial HIV screen positive test. The timing and components of the One4All intervention versus SOC are presented in [Table 1](#).

2.2 Study Design

We adapted and extended an existing deterministic transmission model previously used to estimate the health benefits and costs of expanded HIV screening and ART in the United States [19], British Columbia, Canada [20], and China [21]. Our data sources included results of the CTN-0056 trial, primary analysis of the China National HIV/AIDS Comprehensive Response Information Management System (CRIMS) and published epidemiological and behavioural data to estimate HIV prevalence, incidence, quality-adjusted life-years (QALYs), health care costs and incremental cost-effectiveness ratios (ICERs) associated with the One4All intervention, compared to the standard of care in Guangxi Zhuang Autonomous Region, China, from 2014–2038. A 25-year time horizon was chosen in order to capture potential second-order HIV preventative benefits, however results were reported at 1- and 5-year time horizons as well.

A schematic of the model and dynamics is presented in [Fig 1](#). The adult population of Guangxi aged 15–64 were partitioned into compartments on the basis of HIV risk behavior (men who have sex with men (MSM), injection drug users (IDU), MSM/IDU, and heterosexual (HETERO)), screening status (screened in the past 12 months or not) and HIV infection status. Among those HIV-infected, individuals were further classified as infected, diagnosed, and on ART, and partitioned according to CD4 cell count ($CD4 \geq 500$ cells/mm³, 350–499, 200–349, <200). Health state transitions occurred at monthly intervals. It is important to note that our model captures individuals that are both infected and never diagnosed (the second ‘column’ of compartments in [Fig 1](#)), and diagnosed but not engaged in treatment (third column of compartments). We further note that the population of diagnosed patients is dynamic and composed, at any given time, of ART-experienced and ART-naïve PLHIV.

We simulated the HIV epidemic by first instantiating the risk group size and HIV prevalence levels based on Guangxi data in 2010, and population figures from the Guangxi Statistical Yearbook and 2010 Guangxi census [10,22], thus using 2011–2014 as an instantiation period for the model. We calibrated our model to replicate observed annual diagnoses by adjusting the ratio of monthly screening rate for high (IDU, MSM and IDU/MSM) versus low (HETERO) risk group in compartment i (ψ_i^h / ψ_i^l). We also calibrated our model to match the observed number of PLHIV on ART in Guangxi by adjusting the rate at which an individual in diagnosed compartment i entered treatment at a given CD4-based state of disease progression at time t (φ, α_{it}).

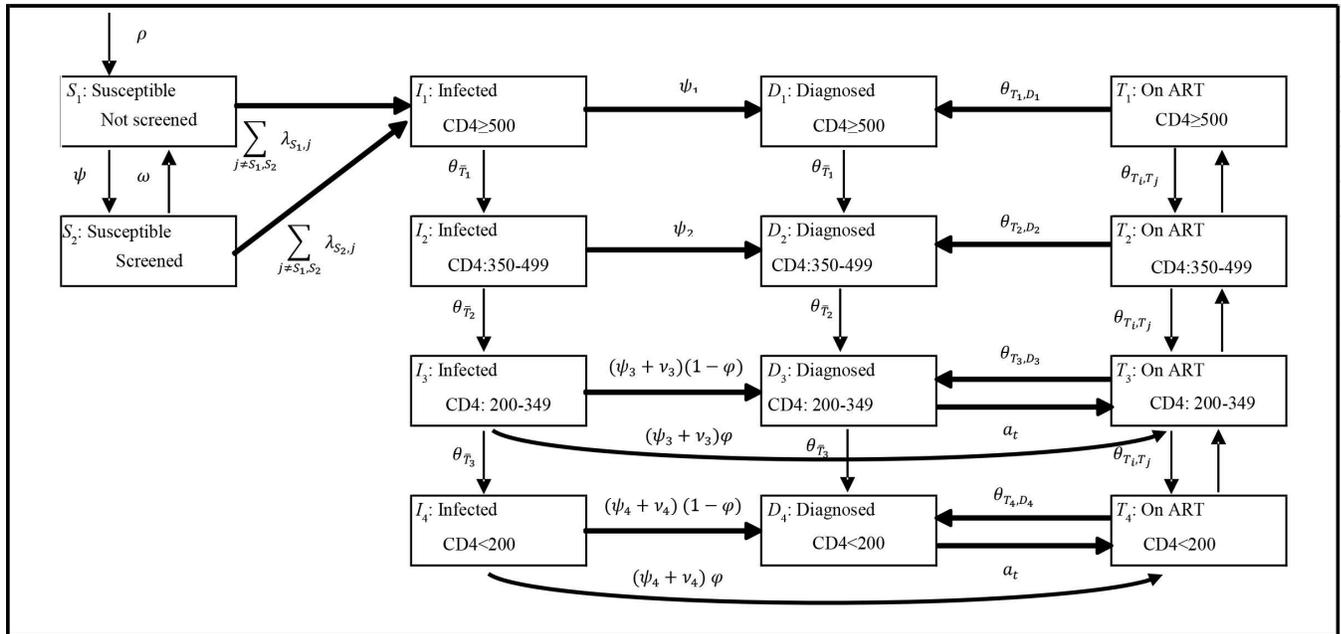


Fig 1. Model Diagram.

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Following calibration to match the known annual number of HIV diagnoses and total number of PLHIV on ART, the model was validated to ensure key epidemiological parameters approximated known or externally-estimated figures. We focused on the size of the HIV-negative population (aged 15–64), the total number of diagnosed cases, and the annual number of deaths among diagnosed PLHIV.

Cost-effectiveness analysis was conducted in accordance with well-established guidelines on cost-effectiveness analyses and dynamic transmission modeling [23]. We considered a public health system perspective. All costs were presented in 2014 Chinese Yuan Renminbi (Chinese currency, USD1 = CNY 6.20 in year 2014), and discounted costs and QALYs at an annual rate of 3%. Key parameters are presented in Table 2, with further detail regarding model construction, parameterization, calibration and validation provided in S1 Appendix.

2.3 Integrating CTN-0056 trial results

The primary outcome of the trial was integrated into the model through the parameter ψ (Fig 1), capturing the increase in the adjusted odds of test receipt within one month in the One4All cohort, compared to the standard of care. The effect of the intervention was adjusted for individual and hospital-level effects using a generalized linear mixed effects regression framework (log link, beta distribution, controlling for hospital-level random effects) [70], and was implemented among HIV-infected heterosexuals with CD4 < 350, mirroring the study population. This effect (odds ratio of 21.78) was converted to a relative risk (3.45) and entered multiplicatively with the base HIV testing rate model parameter, following standard practice [52]. The effect of the intervention was implemented as incremental to the base-case, or standard of care, which was the calibrated representation of the Guangxi HIV/AIDS epidemic at the time of trial initiation (2014). The costs of the One4All intervention were higher than the current standard of care (CNY 2,182 vs. CNY 846), accounting for the higher costs of POC CD4 testing and an additional viral load test.

Table 2. Model parameter estimates.

Variable	Values	References
Population Demographics		
Initial population (aged 15–64):	31,832,050	[22]
IDU	293,551	[24]
MSM	326,797	[25]
MSM/IDU	28,417	[26]
HETERO	31,183,285	Calculated
Initial HIV prevalence (%):	97,114	[9]
IDU	27,349	[27]
MSM	12,418	[28,29]
MSM/IDU	2,648	[28,29]
HETERO	54,699	[30]
Initial no. of HIV diagnosed (including on ART):	50,001	Guangxi CDC
IDU	14,566	Guangxi CDC
MSM	4,595	Guangxi CDC
MSM/IDU	980	Guangxi CDC
HETERO	29,861	Guangxi CDC
Initial no. on ART:	14,749	Guangxi CDC
IDU	2,563	Guangxi CDC
MSM	315	Guangxi CDC
MSM/IDU	25	Guangxi CDC
HETERO	11,846	Guangxi CDC
Monthly mortality rate for individuals:		
Monthly mortality rate (background) (aged 15–64 years)		
HETERO or MSM	0.00021	[10,22]
IDU or MSM/IDU	0.00232	[21]
Monthly mortality rate (background) (aged 65–95 years)	0.00326	[10,22]
Monthly mortality rate (HIV infected and diagnosed)		
HETERO or MSM		
Asymptomatic (CD4: ≥ 350)	0.00225	Calculated, [21]
Symptomatic (CD4: 200–349)	0.00600	Calculated, [21]
AIDS (CD4: < 200)	0.02120	Calculated, [21]
IDU or MSM/IDU		
Asymptomatic (CD4: ≥ 350)	0.00441	Calculated, [21]
Symptomatic (CD4: 200–349)	0.00826	Calculated, [21]
AIDS (CD4: < 200)	0.02387	Calculated, [21]
Monthly mortality rate (on ART)		
HETERO or MSM		
CD4: ≥ 500	0.00049	Appendix
CD4: 350–499	0.00052	Appendix
CD4: 200–349	0.00063	Appendix
CD4: < 200	0.00268	Appendix
IDU or MSM/IDU		
CD4: ≥ 500	0.00261	Calculated
CD4: 350–499	0.00264	Calculated
CD4: 200–349	0.00275	Calculated
CD4: < 200	0.00485	Calculated
Monthly maturation rate	0.00058	[10,22]

(Continued)

Table 2. (Continued)

Variable	Values	References
Monthly entry rate (background)	0.00179	[10,22]
Sexual Transmission		
Transmission probability per partnership:		
Heterosexual:		
CD4: ≥ 500	0.030	[21,31,32,33,34,35,36]
CD4: 350–499	0.030	[21,31,32,33,34,35,36]
CD4: 200–349	0.040	[21,31,32,33,34,35,36]
CD4: < 200	0.080	[21,31,32,33,34,35,36]
Homosexual:		
CD4: ≥ 500	0.040	[21,37,38,39,40]
CD4: 350–499	0.050	[21,37,38,39,40]
CD4: 200–349	0.050	[21,37,38,39,40]
CD4: < 200	0.100	[21,37,38,39,40]
Annual same-sex partners (N)	5	[41]
Annual opposite-sex partners (N):		
IDU	3	[42]
MSM	0.3	[43]
MSM/IDU	0.3	[43]
HETERO	1.2	[30]
Condom use with same-sex partners:		
MSM	46.40%	[27]
MSM/IDU	46.40%	[27]
Condom use with opposite-sex partners:		
IDU	38.30%	[44]
MSM	29.50%	[45]
MSM/IDU	29.50%	[44,45]
HETERO	11.00%	[41]
Condom effectiveness	0.80	[46,47,48]
Injection Drug Use Transmission		
Transmission probability per shared injection:		
CD4: ≥ 500	0.002	[20,21,49,50]
CD4: 350–499	0.002	[20,21,49,50]
CD4: 200–349	0.003	[20,21,49,50]
CD4: < 200	0.003	[20,21,49,50]
Average injections per year	200	[19,21,42]
Fraction of injections that are shared, %	26.40%	[27]
HIV Screening		
Monthly HIV screening rate:		
High risk (IDU or MSM)	Time-varying	Calibrated
Low risk (HETERO)	Time-varying	Calculated, [51]
One4All intervention screening rate multiplier	3.45	One4All, [52]
Monthly probability of symptom-based case-finding:		
High risk (CD4: < 200)	0.00923	[21,53]
Low risk (CD4: 200–349)	0.02082	[21,53]
Reduction in partner numbers among diagnosed (HIV)	0.20	[21,54]
Reduction in partner numbers among diagnosed (AIDS)	0.90	[21]
Antiretroviral therapy		

(Continued)

Table 2. (Continued)

Variable	Values	References
Rate of ART entry from diagnosed compartments	Time-varying	Calibrated
Fraction of individuals from infectious to start ART	0.3	[21,55]
Reduction in injection infectivity due to ART	0.50	[19,53]
Reduction in sexual infectivity due to ART:		
Same sex	0.90	[21,37,38,39,40]
Opposite sex	0.90	[21,37,38,39,40]
HIV disease progression rates for individuals not on ART		
CD4 ≥ 500 to CD4: 350–499	0.02209	[20,53,56,57,58]
CD4: 350–499 to CD4: 200–349	0.02209	[20,53,56,57,58]
CD4: 200–349 to CD4: <200	0.02209	[20,53,56,57,58]
CD4: <200 to Death	0.00250	[20,53,56,57,58]
HIV disease progression rates for individuals on ART		
Health-Related Quality of Life		
Susceptible	0.08333	
Infected: CD4: ≥ 500	0.07500	[21,53,59,60,61,62]
Infected: CD4: 350–499	0.06583	[21,53,59,60,61,62]
Infected: CD4: 200–349	0.06583	[21,53,59,60,61,62]
Infected: CD4: <200	0.06000	[21,53,59,60,61,62]
Diagnosed: CD4: ≥ 500	0.07083	[21,53,59,60,61,62]
Diagnosed: CD4: 350–499	0.06000	[21,53,59,60,61,62]
Diagnosed: CD4: 200–349	0.06000	[21,53,59,60,61,62]
Diagnosed: CD4: <200	0.05667	[21,53,59,60,61,62]
On ART: CD4: ≥ 500	0.07083	[21,53,59,60,61,62]
On ART: CD4: 350–499	0.06917	[21,53,59,60,61,62]
On ART: CD4: 200–349	0.06917	[21,53,59,60,61,62]
On ART: CD4: <200	0.06833	[21,53,59,60,61,62]
IDU multiplier	0.90	[20,63,64]
Costs (2014 CNY)		
Monthly non-ART healthcare cost for non-IDU:		
CD4: ≥ 350	2,029	[21,65]
CD4: 200–349 untreated	3,350	[21,65]
CD4: 200–349 treated with ART	2,996	[21,65]
CD4: <200 untreated	4,491	[21,65]
CD4: <200 treated with ART	3,916	[21,65]
Monthly non-ART healthcare cost for IDU:		
CD4: ≥ 350	4,830	[20,66]
CD4: 200–349 untreated	7,974	[20,66]
CD4: 200–349 treated with ART	7,131	[20,66]
CD4: <200 untreated	10,689	[20,66]
CD4: <200 treated with ART	9321	[20,66]
Monthly cost of ART	221	Guangxi CDC
Monthly healthcare costs for HIV negatives:		
IDU or MSM/IDU	196	[20,21,66]
MSM	78	[20,21,66]
HETERO	82	[20,21,66]
Cost of HIV ELISA antibody test	24	Guangxi CDC
Cost of POC* HIV screening test	24	Guangxi CDC

(Continued)

Table 2. (Continued)

Variable	Values	References
Cost of confirmatory western blot test	500	Guangxi CDC
Cost of behavior counselling	82	[21,67]
Cost of CD4 count test	240	[21,67]
Cost of POC* CD4 count test	576	[68,69]
Cost of plasma viral load test	1500	Guangxi CDC
Annual discount rate, %	3	[21]

* POC represents 'point-of-care' in the proposed One4All screening intervention

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2.4 The force of HIV infection

We incorporated HIV transmission through heterosexual sexual contact, homosexual sexual contact and needle sharing associated with injection drug use. Heterosexual sexual contact occurs within risk groups (for example, both partners are heterosexual, both are injection drug users) and across groups (for example, a (female) injection drug user with a (male) heterosexual, or a (female) heterosexual with an MSM partner). We assumed proportional mixing, in which individuals could be infected by those of other risk groups, but the probability of infection was proportional to the level of contact (sexual or injection) between groups. Parameters dictating HIV risk behaviors were allowed to change over time according to proxies of injection and sexual risk behavior—specifically, rates of methadone maintenance treatment (MMT) uptake and non-HIV sexually transmitted disease [71] during the study period. The model also accounts for changes in risky behavior due to effective HIV screening and counseling [54].

2.5 Disease progression

Disease progression was differentiated among those on ART and not on ART, and estimated as a function of CD4 count, stratified into the four categories noted above. We derived monthly transition rates from population-level registry data held by the NCAIDS, China CDC using a multivariate multi-state Markov model [72]. The methodology allowed for transitions out of treatment, in addition to CD4 improvement and deterioration in treatment (as indicated by arrows in Fig 1). Otherwise, individuals progressed according to the natural history of HIV, for which transition rates were drawn from the published literature [56].

2.6 Costs and quality adjusted life years

Healthcare costs considered in this study included costs of delivering HIV testing in the two comparative arms, costs for ART regimen and non-ART medical care among the entire population. The costs of delivering the 'standard of care' and 'One4All' trial interventions were estimated from trial data. Otherwise, ART and non-ART medical care among PLHIV were estimated from published sources [21]. We applied QALY weights derived from the peer-reviewed literature for HIV-negative individuals and PLHIV in and out of treatment, adjusting for injection drug use [59,60,61,62,73] (further details in S1 Appendix).

2.7 Sensitivity analysis

We considered alternative scenarios to test structural and parameter uncertainties within the model (pertaining to movement in the model, and the point estimates of parameters dictating

these movements, respectively), as well as the sensitivity of the results to the scale and effectiveness of the trial. First, alternate scenarios were constructed to determine the sensitivity of results to parameters estimated with the greatest level of uncertainty, including the proportion of MSM among susceptible population, number of IDU among susceptible population, and baseline HIV prevalence, respectively. Alternate values for key parameter estimates were drawn from the peer-reviewed literature representing alternate estimates, or national (as opposed to Guangxi Regional) estimates. Second, model results were estimated at both the upper and lower bound of CTN-0056 trial's primary outcome, the adjusted odds ratio of screening completeness. Third, alternate fitted curves were utilized to alter baseline constant prediction for time-varying parameters. Forth, we considered alternate scenarios whereby the intervention was able to reach a broader population of PLHIV, including MSM, IDU and MSM/IDU whose CD4 counts were below 350 cells/mm³. Finally, we executed a threshold sensitivity analysis, varying the primary outcome of the trial within the feasible range of odds ratios (1,∞) on the adjusted measure of effect estimated in the trial. Intuitively, this provides us with information on the thresholds at which the One4All intervention would be deemed cost-inefficient relative to the current standard of care. A full description of all sensitivity scenarios is presented in Table A9 in [S1 Appendix](#).

2.8 Ethics Statement

This modeling study has received institutional ethical approval from the University of British Columbia (UBC-PHC approval number: H14-02140).

Results

The CTN-0056 trial recruited a patient population consisting of 97% heterosexuals, 75% of which were male, and 75% over the age of 45. Among those receiving a CD4 test, median CD4 cell counts were 122 and 143.5 for One4All and SOC, respectively [12]. As such, our baseline comparison introduced the effect of the One4All intervention in only HIV-infected heterosexuals with CD4 count < 350.

The full list of parameters used in the model is presented in [Table 2](#). The analysis was parameterized using data from a number of sources, including disease registry data from the NCAIDS, China CDC, the One4All trial, and the published literature. The primary outcome of the trial, the adjusted odds of completeness of HIV screening within 30 days, estimated to be 21.78 (95% CI: 3.81, 124.46), was converted to relative risk 3.45 (95% CI: 2.22, 3.82) and incorporated into the model directly.

The model was calibrated to match the number of new diagnoses, and the number of PLHIV accessing antiretroviral therapy (ART) in a given calendar year between 2011 and 2014, and produced valid estimates of all-cause deaths among PLHIV, and the estimated size of the susceptible population during the calibration period (results presented in [S1 Appendix](#)).

If expanded to the entire region of Guangxi, we estimate the One4All intervention would lead to a reduction of 39 incident HIV cases in the first year, and a total of 802 cases, 0.5% of the expected 171,923 incident cases in the standard of care (SOC) scenario over the 25-year study period. Further, we estimated decreases of 45 deaths in the first year, and 1629 deaths over the 25-year time horizon, translating into a decrease of 1.6% in the probability of mortality among PLHIV in Guangxi over the 25-year study period ([Table 3](#)).

Within a 5-year time horizon the One4All intervention was a dominant strategy. The additional costs of ART (an increment of CNY 6.2 million) were offset by savings of CNY 17.5 million in non-ART medical costs, which incorporated the higher costs of the One4All screening algorithm. With an incremental gain of 409 QALYs, accumulating primarily via delayed

Table 3. Results of cost-effectiveness analysis.

	Incident cases	Deaths among PLHIV	ART costs	Non-ART costs	Total costs	QALYs	ICER
			2014 Million CNY	2014 Million CNY	2014 Million CNY	Million	2014 CNY
1-year time horizon							
Standard of care	5,944	5,285	102.46	4,921.04	37,682.24	32.64	
One4All*	5,905	5,240	103.50	4,923.54	37,685.79	32.64	259,978
One4All_All*	5,806	5,203	104.33	4,921.86	37,685.00	32.64	91,970
5-year time horizon							
Standard of care	28,184	20,582	577.91	22,705.76	179,643.60	156.27	
One4All*	27,885	20,018	589.83	22,684.93	179,635.39	156.27	Dominant
One4All_All*	27,515	19,823	593.93	22,652.18	179,607.98	156.27	Dominant
25-year time horizon							
Standard of care	171,923	103,519	2889.32	99,970.77	738,246.57	635.18	
One4All*	171,121	101,890	2940.29	100,122.22	738,459.09	635.20	11,678
One4All_All*	169,578	101,075	2948.51	99,930.02	738,291.06	635.21	1,690

* *One4All* represents intervention scenario whereby One4All screening intervention was only applied to heterosexual PLHIV, corresponding to trial study population. *One4All_All* represents sensitivity scenario whereby One4All intervention was expanded to all PLHIV from all risk groups.

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mortality, One4All was a dominant strategy (ie. lower costs, higher QALYs gained). In a 25-year time horizon, as a result of the increased duration of life among those diagnosed, both ART (an increment of CNY 51.0 million) and non-ART medical costs (an increment of CNY 136.5 million) were greater in the One4All strategy. With an estimated gain of 18,199 QALYs, we estimated an ICER of 11,678 CNY per QALYs gained. With a current GDP per capita of CNY 49,351 [74], the One4All strategy is highly cost-effective, according to the World Health Organization (WHO) standards [75] (Table 3).

We executed a series of one-way sensitivity analyses focusing on parameters with the greatest degree of uncertainty to determine their effect on the estimated ICER over a 25-year time horizon. Given the fairly modest epidemiological impact of One4All, and the fact that these changes were applied to both strategies, the ICER varied little across sensitivity analyses. Using the lower bound of the UNAIDS estimate for HIV/AIDS prevalence in Guangxi (80,000, as opposed to the baseline prevalence of 97,000) resulted in the most substantial change amongst all sensitivity scenarios, with an ICER of 9,734 CNY per QALY gained, while the highest ICER, screening intervention effectiveness at lower bound, was only slightly higher than 12,000 CNY/QALY, well within a 'highly cost-effective' range. (Fig 2)

If the One4All intervention could reach all risk groups, it could result in a 1.36% reduction in HIV incidence and a 2.36% reduction in mortality among PLHIV, for a cost of 1690 CNY per QALY gained over a 25-year timeframe (Table 3).

Finally, we found that One4All remained cost-effective and highly cost-effective at even minimal levels of effectiveness (odds ratio 1.01 and 1.025, respectively) in HIV testing uptake, further supporting our results.

Discussion

Using a validated dynamic HIV transmission model synthesizing a wealth of data characterizing the HIV/AIDS epidemic in Guangxi, China, we found the One4All HIV testing intervention to be a highly cost-effective strategy to increase HIV test receipt and subsequent ART engagement. Projected over a 25-year timeframe, if the intervention was to be expanded across the province, we estimated One4All would result in declines of 0.5% and 1.6% in HIV

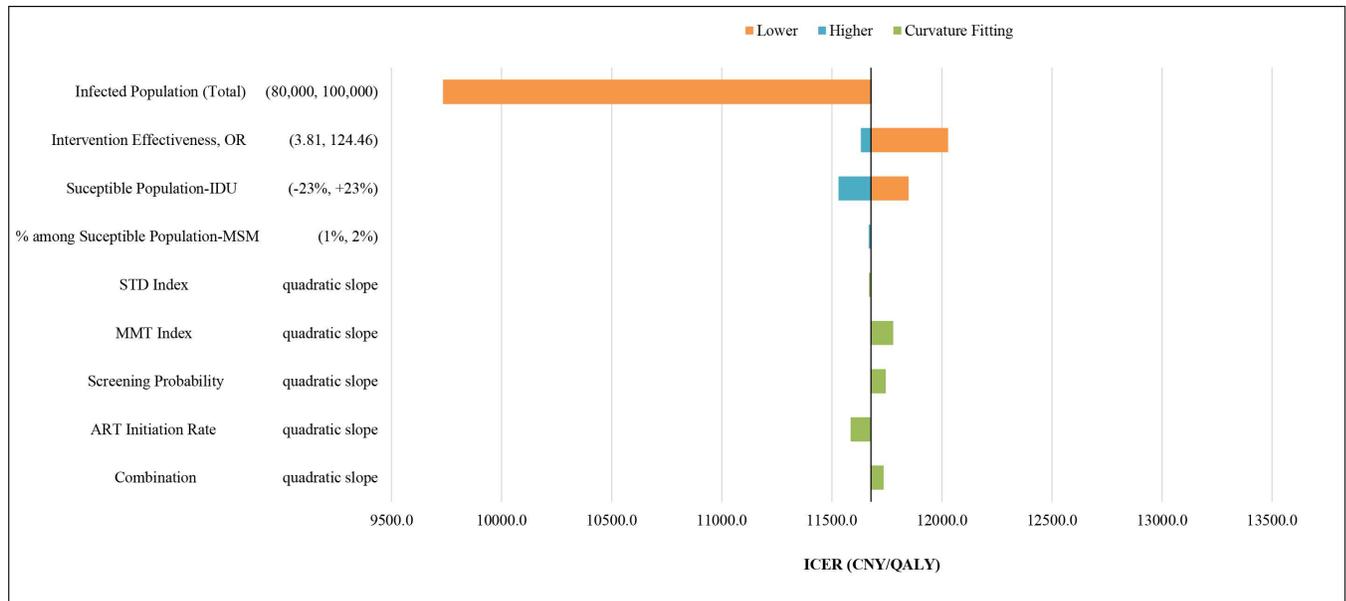


Fig 2. One-way Sensitivity Analyses Plot—Tornado Diagram Estimating Sensitivity of Baseline Results to Uncertain Parameters. Baseline model: (1) 97114 total PLHIV at baseline; (2) Intervention effectiveness, OR = 21.78; (3) 293551 susceptible IDUs; (4) MSM: 1.116% among susceptible population; (5) Constant estimates as year 2014 for STD index, MMT index, annual screening probability and annual ART initiation rate since year 2015.

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incidence and mortality among PLHIV, respectively, increasing to 1.36% and 2.36% if the intervention could extend to populations of MSM and IDU. Sensitivity analyses supported the robustness of the results, and demonstrated that One4All is likely to remain cost-effective in practice even if the real-world odds or HIV test receipt are lower than observed in the trial.

While the One4All intervention undoubtedly represents a much-needed enhancement to Guangxi HIV testing and ART engagement protocols, if implemented, the estimated impact on the HIV epidemic is expected to be modest, with minimal influence on HIV transmission. This should come as little surprise, as it remains a 'passive' intervention, in that undiagnosed cases are not actively sought out for testing. Thus, while optimizing mechanisms to 'test and treat', the intervention does not actively seek out undiagnosed cases, and downstream ART retention is not addressed. Furthermore, the trial recruited primarily older male heterosexuals at late stages of disease progression. While reductions in morbidity and mortality are certainly possible in such populations, declines in HIV transmission are likely to be limited, as projected by our model.

Expanding the scope of the intervention to reach individuals at earlier stages of disease progression would entail integrating the testing algorithm into outpatient and preventative care settings. For instance, the very low number of IDU recruited into CTN-0056 suggests that people who inject drugs do not access care through the typical pathways in Guangxi. Using the One4All algorithm, HIV testing could be delivered in methadone maintenance treatment facilities, similar to other settings internationally [76,77]. Otherwise, home, community-based and mobile testing units, among other modes of outreach-oriented testing campaigns have proven cost-effective in settings with moderate and high undiagnosed HIV prevalence [19,78,79].

The One4All intervention should be considered an integral component of a comprehensive HIV prevention and treatment strategy that would also include more active modes of HIV testing to reach undiagnosed populations at earlier stages of disease progression, and in marginalized or hard-to-reach populations, as well as efforts to optimize ART engagement and

retention. The concept of combination implementation [80,81,82,83,84] has been introduced to capture the need for pragmatic, evidence-based prevention strategies in real-world settings. An economic modeling framework can inform public health investment in the optimal mix of strategies that provide the greatest health benefits, both across regions and over time [85].

This analysis was not without limitations. First, similar to other models used in cost-effectiveness analyses of HIV screening and treatment [86], infectivity was modeled indirectly through CD4-based disease progression stages. Second, while the probability of transmission in early HIV infection was not modeled explicitly, its long-term impact on reduction of incidence was determined to be minimal [87], and is not likely to influence the intervention under study. Third, while the total susceptible population in Guangxi was reproduced accurately, in- and out-migration of PLHIV is not observed, and was implicitly assumed to be equal to zero. Fourth, while drug resistance was not explicitly modeled in our study, it was accounted for in that the cost and disease progression estimates were derived from statistical analyses and published sources that captured the full population of Guangxi PLHIV, including those with multi-drug resistance. Finally, a full probabilistic sensitivity analysis was not executed, and indeed is not recommended in dynamic transmission modeling due to the implicit objective nature of model calibration to actual practice [23].

The One4All testing algorithm increased the probability of HIV test receipt, and thus accelerated ART uptake among those presenting to hospital in 6 study sites in Guangxi Zhuang Autonomous Region, China. Implementing the strategy in hospitals across the region would be highly cost-effective, but best implemented alongside other public health strategies to seek, test, treat and retain people living with HIV/AIDS.

Supporting Information

S1 Appendix.
(DOCX)

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