Supplemental Digital Content – Delaney et al.

Using a multi-test algorithm to improve the positive predictive value of rapid HIV testing and linkage to HIV care in non-clinical HIV test sites.

1. Methods
    a. Matching procedures for linking HIV testing database to the HIV surveillance case registry

    b. Definition of laboratory evidence of HIV care

    c. Modeling Strategy details
        i. Figure 1: Directed Acyclic Graph used to formulate modeling strategy
2. Results
    a. Table 1: Complete list of variables included in models 1-4 as described in the main text and their effects in each model

    b. Table 2: Effect Modification assessment for Model 2: Effects of the rapid test algorithm intervention on the probability of laboratory indications of being in HIV care within 90 days of a positive HIV test, stratified by risk group and prior HIV diagnosis.

    c. Figure 2 Modification of the effect of the RTA and returning to receive confirmatory results and referral when stratified by risk group for MSM compared to other risk groups

Methods:

Matching procedures linking the HIV testing database to the HIV surveillance case registry

The process of linking the HIV testing database to the HIV surveillance case registry was conducted in August 2009 to allow a six-month period to account for time lags between testing and data reporting in both databases. Matching occurred in 2 phases. First, a testing client was determined to be a true match to the eHARS surveillance database if he/she matched on 1) full name and month and year of birth, or 2) date of birth, first initial and an alphanumeric identifier created by the eHARS system from the client's surname. Records for the clients who did not initially match were then manually reviewed; testing sites, test dates, and test identification numbers were used to attempt to match these records to eHARS. For all clients whose testing and eHARS information could be matched, HIV viral load results were extracted from eHARS and added to the data from the testing system.

Definition of laboratory evidence of HIV care

Laboratory data maintained within eHARS contain only the month and year in which a reported laboratory test was performed. For this analysis, laboratory test dates extracted from these systems were modified to be the last day of the month in which they were performed. A viral load test result after the date of testing was considered evidence of HIV care. Clients for whom the first reported VL result was greater than 180 days after their HIV test date were censored. Clients with VL results in the eHARS system reported prior to the HIV test date, indicating previous linkage to care at some point in the past, (n=167, including 56/126 (44%) of those who self-reported as previously diagnosed as HIV-positive and are listed as such in Table 3) were flagged and the first VL result after the HIV test date was used to calculate time to care. Clients with a case report but no reported laboratory results in the eHARS surveillance registry were considered not linked to care, and the time-to-care variable was censored at 180 days after their HIV test date. Clients listed as HIV-infected in the testing database who did not have an eHARS record, either because they had

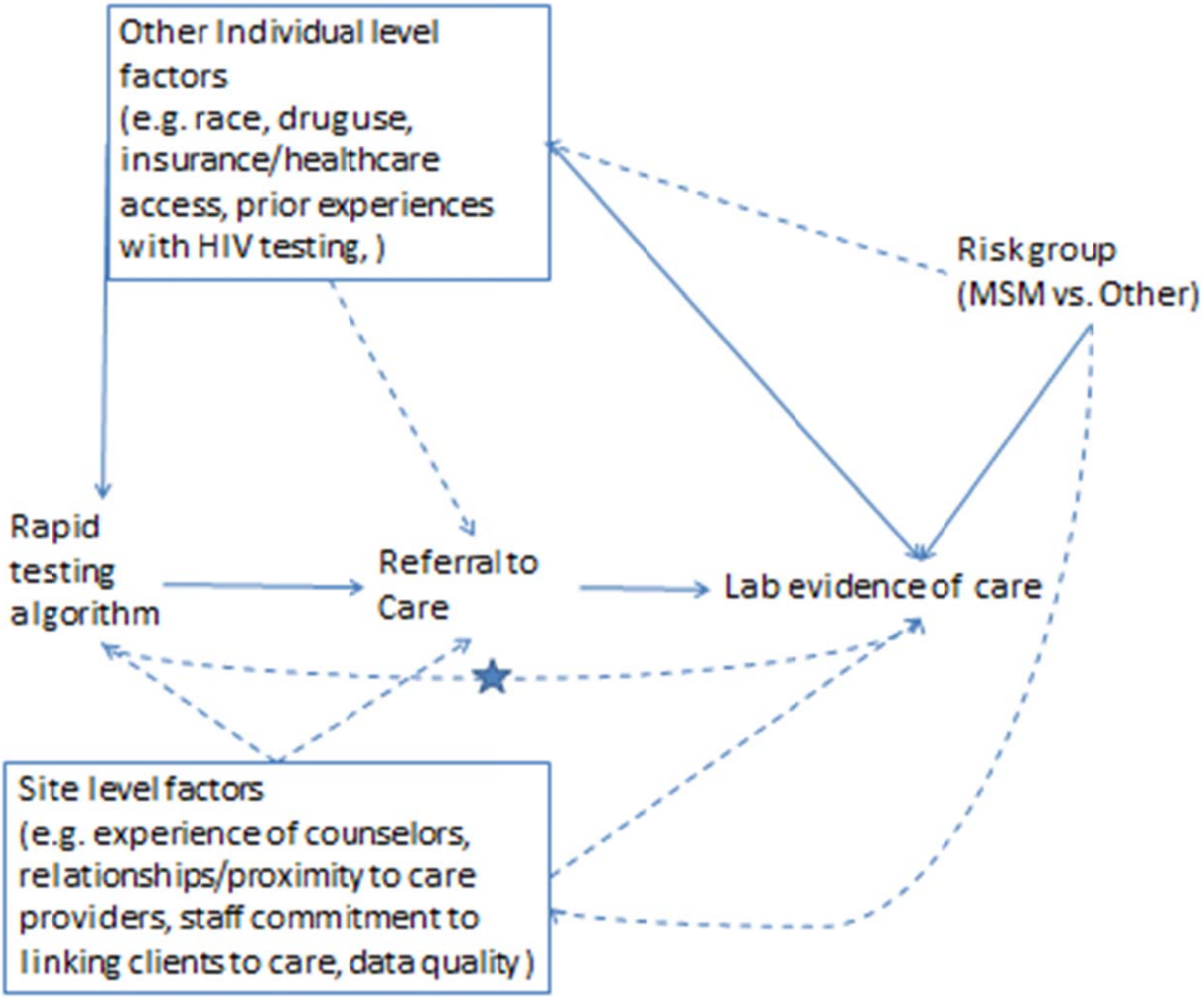
tested anonymously (n=181) or because they were previously diagnosed in a jurisdiction other than San Francisco or Los Angeles (n=48) were eliminated from further analysis (See figure 1 in main text).

Modeling Strategy:

Supplemental Figure 1 shows a Directed Acyclic Graph (DAG) proposed to describe the causal relationship between our intervention of interest (the rapid testing algorithm with same day referral to HIV care) and the outcome measure of laboratory evidence of HIV care within 90 days of HIV testing. As for most studies in which randomization is not possible, we acknowledge the existence of both individual and test site-level factors that could confound the association between our intervention and the outcome. We attempted to control for measured individual-level variables through the use of multivariate Poisson risk regression models. Solid lines in the figure indicate proposed causal pathways for which we have included a variable in these models, while dashed lines include hypothesized pathways for which we do not have data, and therefore could not control directly. Because we did not have measures of each of the site-level factors, and models with site included as a fixed effect variable would not converge (presumably due to the small number of RTA clients who tested positive at each of the 9 intervention sites) we attempted to capture variation in site-level factors and unmeasured individual-level factors (such as poverty, and access to health insurance)--that might aggregate at a particular site--through the use of random intercept term for site in all of our models.

It seems clear that one way use of the rapid test algorithm promotes linkage to care is through same-day referral for care, eliminating the need for clients to return to receive this service and thereby eliminating loss-to-follow-up at this stage. Traditional epidemiologic methods would suggest that in order to fully characterize the effect of the intervention, we should not include the effect of intermediates (in this case receipt of results and referral to care) in our model. Model 2 in table 3 of the main text presents results of such a model.

However, we conducted additional analyses to investigate whether there was an effect of the RTA, after controlling for whether or not clients received their confirmatory test result, post-test counseling and a referral to medical care. Model 3 in supplemental Table 1 below included only the effect of receipt of results as the exposure of interest, trying to measure the value of the arrow depicted in the figure that runs between receipt of results and the outcome. If the arrow marked with the blue star did not exist, we would expect that the effect of getting a result in Model 3 should be very similar in magnitude to the effect of the RTA in model 2. The difference between model 2 and model 3 should be the effect of the path indicated with the blue star. However, to assess both whether this path exists and how much it may contribute to the overall effect of the RTA, we must also control for all other (confounding) paths to the outcome. Furthermore, assessment of the effects (direct and indirect) of the RTA on linkage to care are also complicated by what appears to be modification of the RTA effect by risk group —MSM showing no effect of the RTA in crude and multivariate analyses, those with other reported modes of exposure being much more likely to have laboratory evidence of HIV care within 90 days if they were tested using the RTA— which also may be influenced by potential unmeasured confounders. Thus, while we would like to assess both the direct and indirect effects of the RTA as illustrated in supplemental figure 1, it is unclear whether it is valid to decompose the effects of the RTA into indirect effects due to guaranteeing receipt of results and referral as part of the intervention, and a direct effect of the RTA. Although we controlled for likely confounders present in the data available to us, we can not rule out the possibility of residual confounding, such that the differences between models 2-4 may not be directly interpretable as measures of the total direct and indirect effects of the intervention. As a result we consider Model 2 to be the best model of the effect of the RTA intervention overall, but report the results of Model 4 (including the intermediate variable for receipt of results and referral to HIV medical care) in the main text for the purposes of discussion.



Supplemental Figure 1 Directed Acyclic Graph used to develop modeling strategy

Supplemental Materials

Additional results

Supplemental Table 1: Complete list of Poisson risk models and covariates for assessment of factors associated with having laboratory evidence of HIV care within 90 days of a positive HIV test for 775 clients tested in Los Angeles and San Francisco, California, August 2007-March 2009

								Model 1		Model 2		Model 3		Model 4	
		Total		Linked < 90 days		RR[a]	95% CI[b]	aRR1[c]	95% CI	aRR2[d]	95% CI	aRR3[e,f]	95% CI	aRR4[g]	95% CI
		N	%	N	%										
		775	100.0	465	60.0										
Project Area															
	LA	549	70.8	338	61.6	ref.									
	SF	226	29.2	127	56.2	0.91	0.80–1.04								
Risk Group															
	MSM	555	71.6	324	58.4	ref		ref							
	IDU	54	7.0	32	59.3	1.02	0.71–1.46	0.93	0.73–1.18						
	Other	166	21.4	109	65.7	1.13	0.91–1.40	1.12	0.94–1.33						
Race/Ethnicity															
	White	225	29.0	139	61.8	ref		ref							
	Black	196	25.3	113	57.7	0.93	0.80–1.09	0.87	0.77–0.99	0.88	0.77–0.99	0.95	0.84–1.08	0.94	0.84–1.07
	Hispanic	277	35.7	176	63.5	1.03	0.90–1.18	0.96	0.82–1.12	0.98	0.83–1.14	0.99	0.85–1.17	1	0.85–1.17
	Other	77	9.9	37	48.1	0.78	0.60–1.00	0.72	0.57–0.89	0.71	0.58–0.87	0.74	0.61–0.91	0.72	0.60–0.88
Homeless	Yes	61	7.9	41	67.2	1.1	0.94–1.36	1.15	0.97–1.36	1.12	0.95–1.32	1.15	0.99–1.32	1.13	0.97–1.32
	No	714	92.1	424	59.3										
Received Result and Referral	Yes	461	59.5	307	66.7	1.33	1.16–1.51							1.35	1.20–1.51
	No	314	40.5	158	50.3										

Previously Tested	Yes	640	82.6	377	58.9	0.9	0.79–1.03	0.9	0.74–1.11	0.91	0.75–1.09	0.88	0.71–1.07	0.89	0.73–1.08
	No	135	17.4	88	65.2										
Didn't get most recent prior test result	Yes	30	3.9	23	76.7	1.29	1.05–1.59	1.32	1.05–1.66	1.32	1.07–1.63	1.35	1.09–1.67	1.35	1.09–1.67
	Other	745	96.1	442	59.3										
Previously Diagnosed with HIV	Yes	126	16.3	79	62.7	1.05	.90–1.22	1.03	0.91–1.18						
	Other	649	83.7	386	59.5										
Tested with the Rapid test Algorithm (RTA)															
No Interaction model	Yes	179	23.1	111	62.0	1.04	0.91–1.19	1.09	0.98–1.23						
	No	596	76.9	354	59.4										
Interaction with risk group[e]															
	Neither exposed nor MSM	177	22.8	106	59.9	ref				ref					
	MSM but not exposed	419	54.1	248	59.2	0.99	0.79–1.24			1.02	0.89–1.16	0.92	0.76–1.10	1.01	0.89–1.15
	Exposed but not MSM	43	5.5	35	81.4	1.36	0.93–1.99			1.43	1.11–1.84	1.26	1.03–1.54	1.25	0.97–1.62
	Both exposed and MSM	136	17.5	76	55.9	0.93	0.69–1.25			0.98	0.80–1.21	1.19	0.97–1.46	0.87	0.70–1.07

Interaction with self-reported previous diagnosis															
	Not exposed And Not Previously Diagnosed	476	61.4	280	58.8	ref			ref						
	Not exposed And Previously Diagnosed	120	15.4	74	61.7	1.05	0.81–1.36		1.03	0.89–1.20	0.96	0.74–1.24	1.08	0.95–1.22	
	Exposed And Not Previously Diagnosed	173	22.3	106	61.3	1.04	0.83–1.30		1.43	1.11–1.84	1.26	1.03–1.54	1.25	0.97–1.62	
	Exposed And Previously Diagnosed	6	0.8	5	88.3	1.42	0.58–3.44		1.81	1.00–3.28	1.53	1.21–1.93	1.57	0.85–2.89	
Random effect for Study site Mixture Test P-value[h]								0.0075	0.0154		0.2848		0.2213		

a) RR= Relative risk, unadjusted ratio of the probability of having laboratory evidence (at least one HIV-1 viral load reported to HIV surveillance) within 90 days of the study HIV test date, relative to the same probability in the reference category for each characteristic listed in the first column
b) 95% CI = 95% confidence interval
c) aRR1 = Adjusted relative risk, as obtained from a Poisson risk model (23) that included a random intercept for study site; Model 1 includes the main effect of the intervention (rapid test algorithm with same day referral) overall as well as all covariates except an indicator for receipt of results and referral (hypothesized to be an intermediate effect of the intervention on the probability of having laboratory evidence of HIV care within 90 days of the date of HIV testing).
d) aRR2 = Adjusted relative risk for Model 2. The model was exactly the same as Model 1 except it also included multiplicative interaction terms for the effect of the RTA by risk group (categorized as MSM and non-MSM), and a multiplicative interaction term for the effect of the RTA across categories of client self-report of a positive HIV test result prior to the current study HIV test date
e) The definition of exposure changes depending on the model being considered. For models 2 and 4, exposure is to the intervention, the rapid test algorithm with same day referral for HIV care. In model 3, the exposure is receipt of results and referral, either by returning for confirmatory results at a comparison site or by testing at an intervention site

f) aRR3 = Adjusted relative risk for Model 3. All covariates in the model are the same except that the only exposure of interest is receipt of post-test counseling and a referral, either by returning for confirmatory results at a comparison site or by testing at an intervention site, instead of receiving an RTA result. Multiplicative interaction terms in this model are for risk group (MSM vs. non-MSM) and self-report of a prior positive test result and the measure of receipt of results and referral.

g) aRR4 = Adjusted relative risk for Model 4. All covariates listed in the table are included, including multiplicative interaction terms for the RTA across levels of both risk group (MSM v. non-MSM) and self-report of a prior positive test result.

h) Mixture test p-value for the effect of the site random intercept term in each model. Models with $p < 0.05$ indicate significant unexplained heterogeneity in the baseline probability of being in HIV care within 90 days of the HIV test date across study sites.

Supplemental Table 2: Effect Modification assessment, Poisson Risk Model 2: Effects of the rapid test algorithm intervention on the probability of laboratory indications of being in HIV care within 90 days of a positive HIV test, stratified by risk group and prior HIV diagnosis.

	Exposure		
	Tested by RTA	Tested at Comparison site	RTA effect in each subgroup (row)
Risk group			
MSM	1	1.03 (0.89-1.17)	0.98 (0.80 – 1.21)
Other risk groups	1.48 (1.03-1.94)	1.01 (0.80-1.23)	1.43 (1.11 – 1.84)
Relative Excess Risk due to interaction (Measure of Additive interaction)		-0.50 (-0.95 – -0.05)	
Ratio of effect in other risk groups to effect among MSM (Measure of Multiplicative interaction)		1.47 (1.12 – 1.81)	

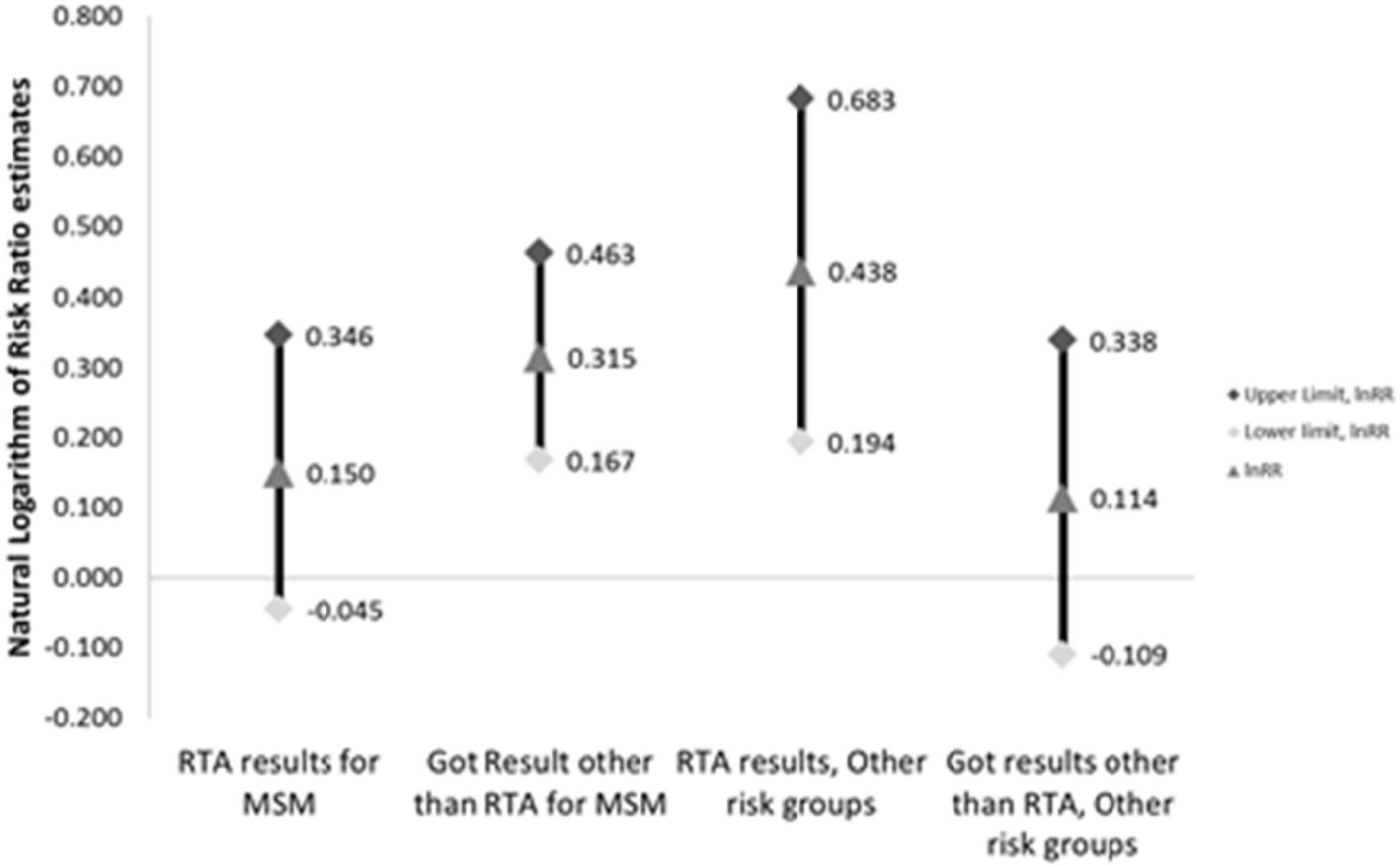
	Exposure		
	Tested by RTA	Tested at Comparison site	RTA effect in each subgroup (row)
Self-reported history of a positive HIV test			
Previously Diagnosed	1.84 (0.75-2.92)	1.08 (0.90-1.26)	1.70 (0.59-2.80)
Not Previously Diagnosed	1.47(1.12-1.81)	1	1.47 (1.12-1.81)
Relative Excess Risk due to interaction		0.29 (-0.85-1.42)	
Ratio of effect in Previously Diagnosed to Effect among those newly diagnosed		1.16 (0.40-1.91)	

This table presents a more detailed analysis of the modification of the effect of the intervention (HIV testing using the rapid test algorithm, with same day referral for those found to be HIV-infected) across strata of both risk group (men who have sex with men (MSM) versus non-MSM (Injection drug users, heterosexual men and women, etc.), and self-report of a prior positive HIV test (prior diagnosis). Effect estimates and confidence intervals in this table differ slightly from those reported in the main text and in Supplemental table 1 because in the main text we used GLIMMIX

procedure in SAS v 9.2 which uses linearization methods based on a pseudo-likelihood function, while here we used NLMIXED which uses an integral approximation by Gauss-Hermite adaptive quadrature for all estimation and is the only procedure n which calculation of the relative excess risk due to interaction and the associated confidence interval can be accomplished directly. Here we see a strong case for effect modification by risk group, with the lowest percentage of persons with laboratory evidence indicating they were in care within 90 days (55.9%, Table 3, main text) occurring among MSM tested at intervention sites. In contrast, the RTA intervention had a strong effect on linkage to care among those not in the MSM risk group (aRR2 1.43, 95% CI: 1.11-1.84). Both the measure of additive and the measure of multiplicative interaction indicate a strong reduction in the effect of the RTA intervention for MSM compared to non-MSM.

For persons who indicated having had a prior history of HIV diagnosis, the RTA had a strong but non-significant effect (aRR2 1.70, 95% CI 0.59 – 2.80). In contrast, for those who had never tested positive before, when used at the testing event captured in the study the RTA intervention increased the probability of having laboratory evidence of being in HIV care within 90 days of testing (aRR2 1.47, 95% CI 1.12-1.81). For the prior history of diagnosis variable, the measures of additive and multiplicative interaction, although indicative of some interaction, had confidence intervals which included their null values.

Modification of the Effect of the rapid test algorithm or receiving confirmed test results on the probability of being in care within 90 days of HIV testing, for MSM versus other risk groups.



Supplemental figure 2 presents the three-way interaction between risk group, receiving HIV testing through the intervention, and receiving test results, on the log-risk scale, such that significant effects are those for which the confidence intervals displayed do not include zero. For both MSM and other risk groups, the reference is those within the group that failed to return for test results. Receipt of results at a comparison site, by returning to the test site to get confirmatory results and a referral to HIV care, significantly improved the probability of being in care within 90 days for MSM, but not for non-MSM. In contrast, receiving test results at an intervention site (therefore receiving the RTA and a same-day referral) significantly improved the probability of being in care within 90 days for non-MSM compared to non-MSM who did not return for their results at comparison sites. For both risk groups, the confidence intervals for effect of receiving results from the RTA overlapped those of receiving results at a comparison site.