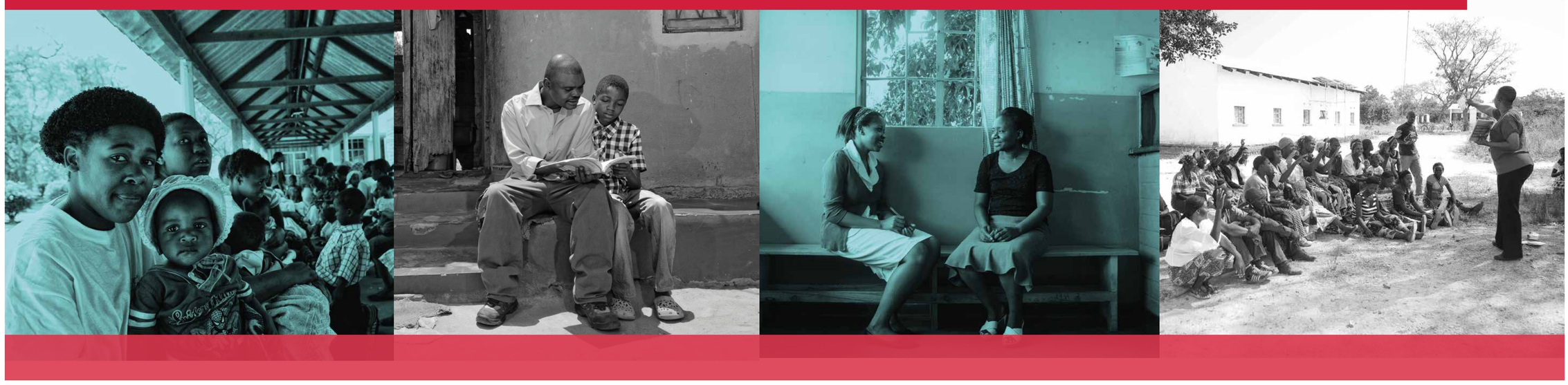

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A clinical utility risk-benefit analysis for HIV self-testing

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BACKGROUND

As countries work to achieve the United Nation's "90-90-90" testing and treatment targets, many countries are adopting WHO's recommendation to offer HIVST as an additional HIV testing approach. Many self-testers can use an HIV rapid diagnostic test (RDT) correctly and achieve results similar to trained testers. Although HIVST does not provide an HIV-positive diagnosis some concern about potential false reactive and false non-reactive self-test results remain. Thus, we conducted a clinical utility risk benefit analysis to establish a minimum performance threshold for HIVST at which public health benefit can be achieved.

METHODS

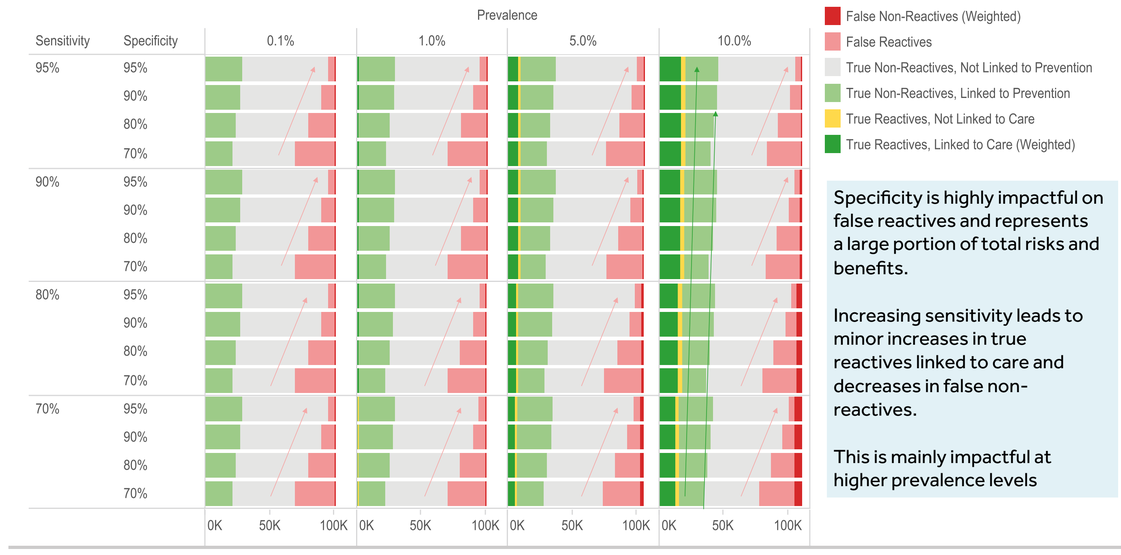
To assess HIVST's clinical utility and weigh performance-related risks and benefits: sensitivity (65-99.8%), specificity (65-100%), HIV prevalence (0.01-15%), linkage to care (50-85%) and linkage to prevention (0-35%) were considered. Ranges were based on literature review and available programmatic data from South Africa. Different scenarios characterized by varying levels of these factors were simulated. We then sampled from distributions to generate each scenario; and re-ran simulations excluding scenarios in which no benefit was achieved. A net benefit score was derived as Total Benefit (calculated as the sum of true reactive linked to care multiplied by three and; the true nonreactive linked to prevention) minus Total Risk (sum of false reactive and; false nonreactive multiplied by two). The weight for false nonreactives, false reactives, true reactives linked to care and true nonreactive linked to prevention were weighted based on expert consultation. The proportion of scenarios with positive net benefit was calculated.

RESULTS

61% of scenarios with ≥70% sensitivity and ≥90% specificity yielded greater benefit than risk. In high prevalence scenarios (prevalence ≥5-10%), positive net benefit was observed at ≥80% specificity and ≥70% sensitivity. For very low prevalence scenarios (prevalence 0.1-1%), net benefit marginally increased when sensitivity increased from 70% to 90%. Linkage to prevention drove net benefit; when moderate (20-30%) benefit was achieved at ≥80% specificity, when low (0-10%) ≥90% specificity was needed. Linkage to care (varied from 50-60% to 70-80%) had modest impact except in very high prevalence settings, e.g. among female sex workers in Johannesburg a positive net benefit in all scenarios was not observed until linkage to care was ≥50%.

Figure 1. Subset of scenarios with net positive results

Base case scenario: Linkage to care 60%; Linkage to prevention 30%

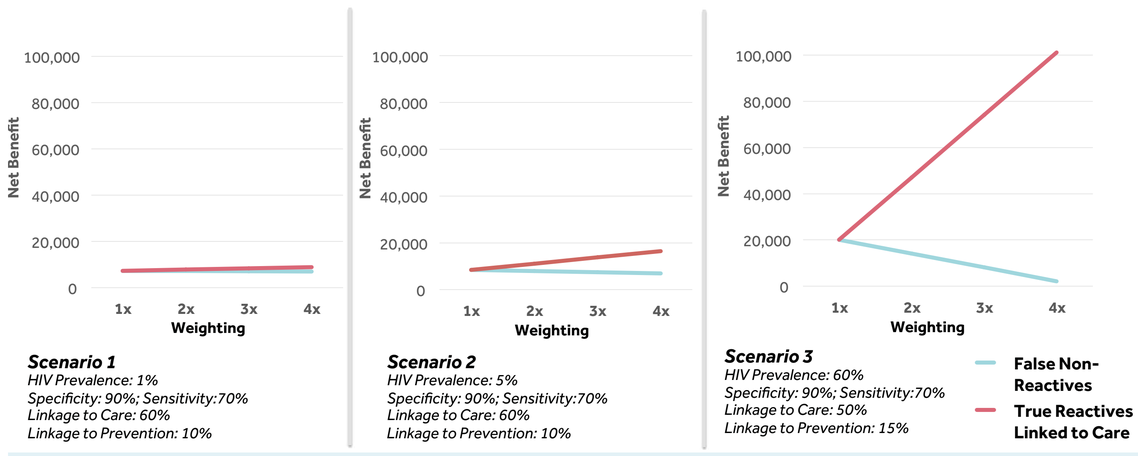


Specificity is highly impactful on false reactives and represents a large portion of total risks and benefits.

Increasing sensitivity leads to minor increases in true reactives linked to care and decreases in false non-reactives.

This is mainly impactful at higher prevalence levels

Figure 2. Varying weights of risk and benefit by HIV prevalence



Changes in the weighting of false non-reactives and true reactives linked to care will impact the net benefit of testing scenario differently depending on characteristics of the scenario, such as HIV prevalence and linkage rates.

Figure 3. Case Example female sex workers in Johannesburg, South Africa

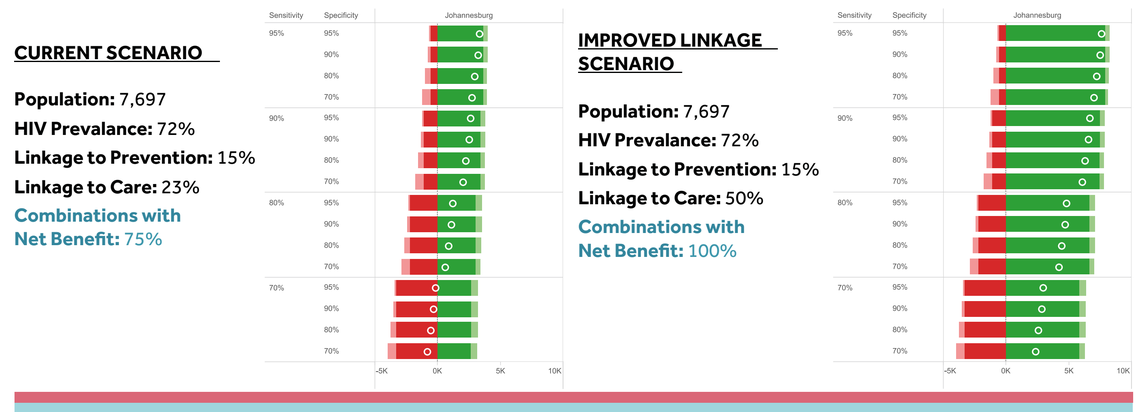


Table 1a. Percent of situations with net positive results, overall

Sensitivity Levels \ Specificity Levels	99%	95%	90%	80%	70%	Total Aggregate
99%	**94%**	**88%**	**78%**	48%	19%	**65%**
95%	**94%**	**88%**	**77%**	47%	16%	**64%**
90%	**94%**	**88%**	**77%**	45%	13%	**63%**
80%	**92%**	**86%**	**72%**	41%	8%	**60%**
70%	**89%**	**81%**	**66%**	36%	3%	**55%**
Aggregate	**93%**	**86%**	**74%**	43%	12%	**61%**

Tables 1a - 2f show a sample of scenarios yielding a net positive benefit within various combinations of sensitivity and specificity.

In Tables 1a-b each combination of sensitivity and specificity contains a sample of 64 scenarios derived through combining four rates of HIV prevalence, four levels of linkage to care and four levels of linkage to prevention.

In Tables 2a-f each combination of sensitivity and specificity contains 32 scenarios derived through combining two rates of HIV prevalence, four levels of linkage to care and four levels of linkage to prevention.

Table 1b. Percent of situations with net positive results, overall (90-100%)

Sensitivity Levels \ Specificity Levels	100%	99%	98%	97%	96%	95%	94%	93%	92%	91%	90%	Total Aggregate
100%	100%	94%	91%	88%	88%	88%	88%	88%	86%	86%	78%	88%
99%	100%	94%	91%	88%	88%	88%	88%	88%	86%	86%	78%	88%
98%	100%	94%	91%	88%	88%	88%	88%	88%	86%	86%	78%	88%
97%	100%	94%	89%	88%	88%	88%	88%	88%	86%	84%	78%	88%
96%	100%	94%	89%	88%	88%	88%	88%	88%	86%	84%	78%	88%
95%	100%	94%	89%	88%	88%	88%	88%	86%	86%	84%	77%	88%
94%	100%	94%	89%	88%	88%	88%	88%	86%	86%	84%	77%	88%
93%	100%	94%	89%	88%	88%	88%	88%	86%	86%	84%	77%	88%
92%	100%	94%	89%	88%	88%	88%	88%	86%	84%	84%	77%	88%
91%	100%	94%	89%	88%	88%	88%	88%	86%	84%	84%	77%	88%
90%	100%	94%	88%	88%	88%	88%	88%	86%	84%	83%	77%	87%
Aggregate	100%	94%	89%	88%	88%	88%	88%	87%	86%	85%	77%	88%

Levels used in combinations:

HIV Prevalence: 0.1%, 1%, 5%, 10%

Rate of Linkage to Care (of Reactive Tests): 50%, 60%, 70%, 80%

Rate of Linkage Prevention (of Non-Reactive Tests): 0%, 10%, 20%, 30%

Tables 2a-f. Percent of situations with net positive results, according to HIV prevalence, linkage to prevention and care

Very Low HIV Prevalence (0.1% and 1%)

Sensitivity Levels \ Specificity Levels	99%	95%	90%	80%	70%	Total Aggregate
99%	**88%**	**75%**	**63%**	25%	0%	**50%**
95%	**88%**	**75%**	**63%**	25%	0%	**50%**
90%	**88%**	**75%**	**63%**	25%	0%	**50%**
80%	**88%**	**75%**	**59%**	25%	0%	49%
70%	**78%**	**75%**	**53%**	25%	0%	46%
Aggregate	**85%**	**75%**	**60%**	25%	0%	49%

High HIV Prevalence (5% and 10%)

Sensitivity Levels \ Specificity Levels	99%	95%	90%	80%	70%	Total Aggregate
99%	**100%**	**100%**	**94%**	**72%**	38%	**81%**
95%	**100%**	**100%**	**91%**	**69%**	31%	**78%**
90%	**100%**	**100%**	**91%**	**66%**	25%	**76%**
80%	**100%**	**97%**	**84%**	**56%**	16%	**71%**
70%	**100%**	**88%**	**78%**	47%	6%	**64%**
Aggregate	**100%**	**97%**	**88%**	**62%**	23%	**74%**

Low Linkage to Prevention (0% and 10%)

Sensitivity Levels \ Specificity Levels	99%	95%	90%	80%	70%	Total Aggregate
99%	**88%**	**75%**	**56%**	22%	3%	49%
95%	**88%**	**75%**	**53%**	19%	3%	48%
90%	**88%**	**75%**	**53%**	16%	0%	46%
80%	**84%**	**72%**	44%	6%	0%	41%
70%	**78%**	**63%**	31%	3%	0%	35%
Aggregate	**85%**	**72%**	48%	13%	1%	44%

Moderate Linkage to Prevention (20% and 30%)

Sensitivity Levels \ Specificity Levels	99%	95%	90%	80%	70%	Total Aggregate
99%	**100%**	**100%**	**100%**	**75%**	34%	**82%**
95%	**100%**	**100%**	**100%**	**75%**	28%	**81%**
90%	**100%**	**100%**	**100%**	**75%**	25%	**80%**
80%	**100%**	**100%**	**100%**	**75%**	16%	**78%**
70%	**100%**	**100%**	**100%**	**69%**	6%	**75%**
Aggregate	**100%**	**100%**	**100%**	**74%**	22%	**79%**

Low/Moderate Linkage to Care (50% and 60%)

Sensitivity Levels \ Specificity Levels	99%	95%	90%	80%	70%	Total Aggregate
99%	**94%**	**88%**	**75%**	44%	16%	**63%**
95%	**94%**	**88%**	**75%**	44%	9%	**62%**
90%	**94%**	**88%**	**75%**	44%	6%	**61%**
80%	**91%**	**84%**	**69%**	38%	6%	**58%**
70%	**88%**	**78%**	**63%**	31%	0%	**52%**
Aggregate	**92%**	**85%**	**71%**	40%	8%	**59%**

High Linkage to Care (70% and 80%)

Sensitivity Levels \ Specificity Levels	99%	95%	90%	80%	70%	Total Aggregate
99%	**94%**	**88%**	**81%**	**53%**	22%	**68%**
95%	**94%**	**88%**	**78%**	**50%**	22%	**66%**
90%	**94%**	**88%**	**78%**	47%	19%	**65%**
80%	**94%**	**88%**	**75%**	44%	9%	**62%**
70%	**91%**	**84%**	**69%**	41%	6%	**58%**
Aggregate	**93%**	**87%**	**76%**	47%	16%	**64%**

CONCLUSION

In the majority of scenarios, risks were exceeded by the benefits of diagnosis and linkage to HIV prevention and treatment services.

While HIVST's clinical utility is greatest when performance is greatest, this analysis suggests **that net benefit can be achieved** even with performance below currently acceptable standards (≥90% specificity and ≥70% sensitivity) in most all settings considered; provided services linking self-testers to HIV prevention and treatment services are **functional**. For very high prevalence settings, such as those among female sex workers in Johannesburg, South Africa (72%), with very low linkage (23%) , ≥90% sensitivity and specificity would be needed to observe a net positive benefit. This emphasizes the need to focus on effective linkage following HIV self-testing, as with all testing services.

The likelihood of achieving a high-level of clinical utility using HIVST should be **high** as studies have shown HIVST kits can achieve sensitivity (80–100%) and specificity (95.1–100%).

LIMITATIONS

This clinical utility analysis assessed HIVST risk and benefit based on performance alone and did not consider additional social benefits or possible harm.

In addition, the weightings utilized in the model were derived from expert opinion due to the absence of sufficient data. We are currently exploring updating this analysis using data from the HIV self-test Africa (STAR) project to more explicitly model the consequences of false reactive and non-reactive, as well as the benefits of correct results.