

Personalized Treatment Adherence Support Strategies for Tuberculosis Patients in Kenya

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With Justin James Boutilier & Erez Yoeli

In collaboration with *Keheala*



Rotman Healthcare Roundtable – March 2020

OM in Global Health — Broad Opportunity

The potential impact is significant

- Life-expectancy in sub-Saharan Africa is 57 years (79 in US)
- Child mortality is 8.3% (0.6% in US)
- HIV prevalence is 9% (0.3% in US)
- Among top-10 killers are Pneumonia, HIV/AIDS, Diarrhoea, TB, Malaria

OR/OM is the relevant approach

- Funds, medicine, and technology are increasingly available — the challenges are operational
- Programs initiated on small cost-effectiveness studies — cost, feasibility, impact at scale?

The time is now

- Data is becoming available
- Healthcare delivery programs are being scaled up and professionalized

The research is interesting

- Health delivery programs in sub-Saharan Africa are structurally different
- Programs are complex and underanalyzed
- Research on extreme conditions can result in useful general insights

Tuberculosis Worldwide

In 2015

10.4 million cases

1.8 million deaths

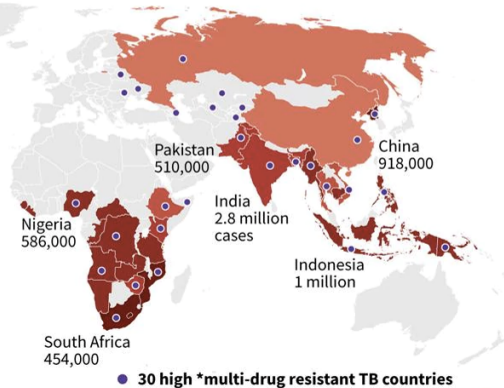
480,000 *MDR-TB cases

30 high-burden countries

Incidence rates, 2015

Estimates, new cases per 100,000 population

- 40 - 99
- 100 - 199
- 200 - 299
- 300 - 499
- 500+



Source : WHO global tuberculosis report 2016

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Tuberculosis Treatment and Challenges

We have the **treatment** but **treatment completion** rates are low, partly for **behavioral reasons**.

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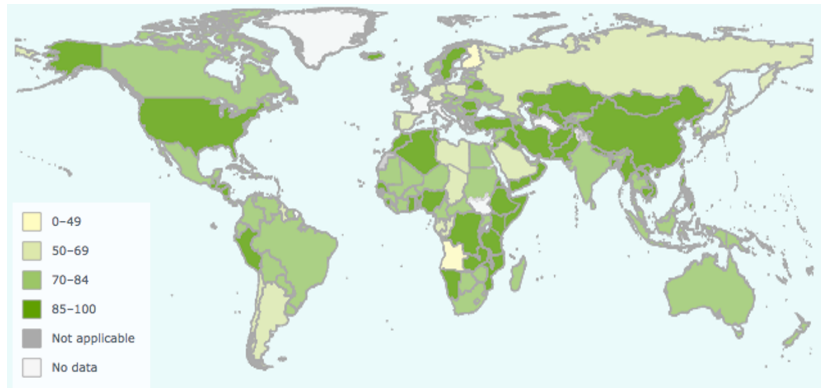
STREPTOMYCIN TREATMENT OF PULMONARY TUBERCULOSIS

A MEDICAL RESEARCH COUNCIL INVESTIGATION

The following gives the short-term results of a controlled investigation into the effects of streptomycin on one type of pulmonary tuberculosis. The inquiry was planned and directed by the Streptomycin in Tuberculosis Trials Committee, composed of the following members: Dr. Geoffrey Marshall (chairman), Professor J. W. S. Blacklock, Professor C. Cameron, Professor N. B. Capon, Dr. R. Cruickshank, Professor J. H. Gaddum, Dr. F. R. G. Heaf, Professor A. Bradford Hill, Dr. L. E. Houghton, Dr. J. Clifford Hoyle, Professor H. Raistrick, Dr. J. G. Scadding, Professor W. H. Tytler, Professor G. S. Wilson, and Dr. P. D'Arcy Hart (secretary). The centres at which the work was carried out and the specialists in charge of patients and pathological work were as follows:

Tuberculosis Treatment and Challenges

We have the **treatment** but **treatment completion** rates are low, partly for **behavioral reasons**.



Tuberculosis Treatment and Challenges

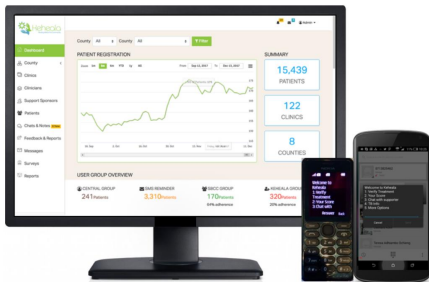
We have the **treatment** but **treatment completion** rates are low, partly for **behavioral reasons**.

- ... takes a long time
- ... significant side-effects
- ... requires frequent clinic visits
- ... has associated stigma





Our Solution



Disease Management Tools reduce the patient burden

Behavioral Interventions from the social sciences maximize adherence and motivation

Non-Stigmatizing Support

Data and Analytics focus limited resources

Accessible by mobile phone without download

Keheala Platform

Treatment Adherence Support

- Patient verification
- Reminders
- Sponsor outreach

Reminders and self-verification

It's time to verify!

USSD Based

- Works on 'dumb phones'
- Only requires network connection

Accountability and support

Hi Jane, it's Jill. I saw that you didn't verify today or yesterday. Is there anything I can do to help?

Based on Behavioral Principles

- Increase observability
- Minimize plausible deniability
- Establish a norm
- Use pro-social motivation

Keheala Platform

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Motivation

Congratulations!
You made the heroes circle!

Congratulations! Together, we're
kicking TB out of Kenya!

Data Source: Keheala RCT

- Design

- 1105 patients
 - 570 on platform
- 17 clinics
- Nairobi, Kenya
- Feb 2016 - Dec 2016

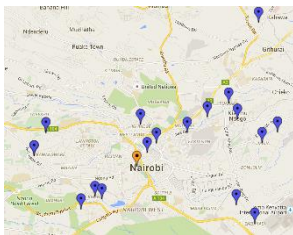
- Data collected

- Patient socio-demographic info
- Health outcomes:
 - Bad: LTFU or D or F
 - Good: TC or C
- Engagement outcomes:
 - Daily verification



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Keheala RCT Outcomes

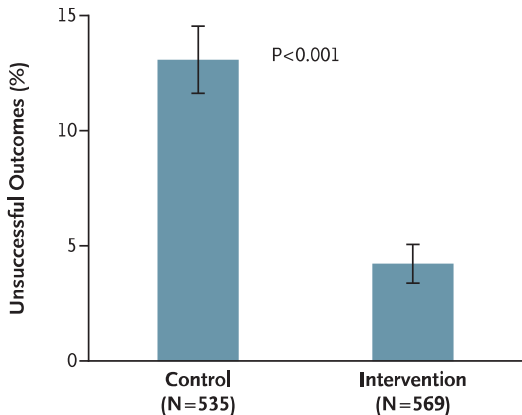


Figure 1. Unsuccessful Treatment Outcomes, According to Trial Group.

Research Questions

Research Objective:

“Develop an implementable policy for personalization of treatment adherence support”

Pre-Enrollment Research Question:

1. Who should be enrolled?
 - Who benefits from treatment adherence support?

} Prediction

Post-Enrollment Research Questions:

1. Does outreach improve engagement?
 - What is the population-level average effect of outreach?
2. Can we identify *at-risk* patients?
 - Who is likely to cease verification?
 - Who is likely to have a bad outcome?
3. Does outreach improve engagement among *at-risk* patients?
 - What is the effect of outreach on *at-risk* patients?

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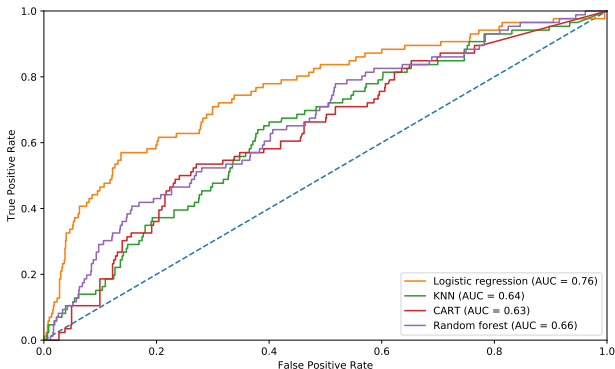
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} Prediction

Pre-Enrollment Personalization

Prediction Accuracy

- Question: Can we predict outcomes?
- Data: Full population (Control: 535, Treatment: 570)
- Outcome: Unsuccessful treatment (LTFU, D, F) vs Successful treatment (C, TC)
- Features: Only demographics, no engagement data *



Pre-Enrollment Personalization

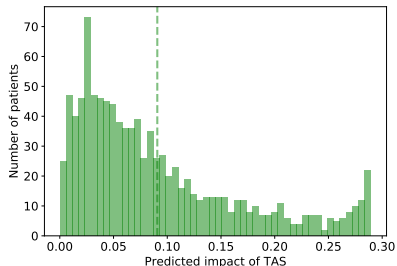
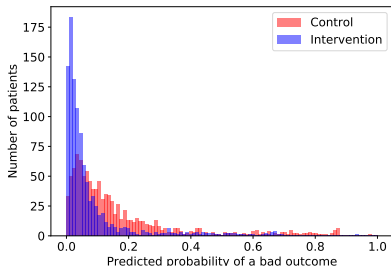
Counterfactuals

- Question: What is the individual impact of Keheala?
- Analysis: Individual outcome prediction with / without Keheala.

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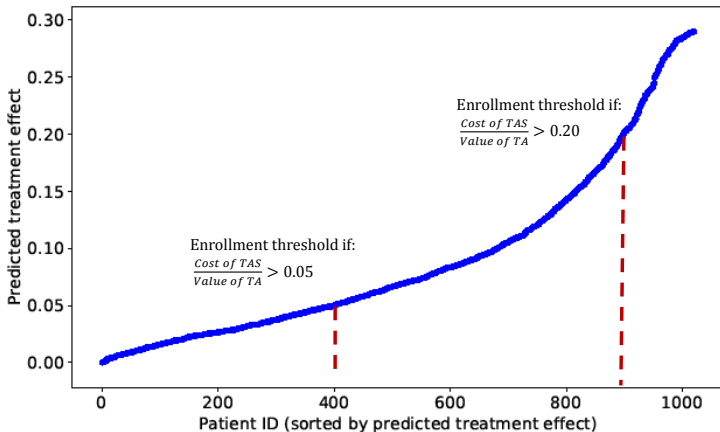
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Pre-Enrollment Personalization

Managerial Implications



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1. Does **outreach** improve **engagement**?
 - What is the population-level average effect of outreach?
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3. Does **outreach** improve **engagement** among **at-risk** patients?
 - What is the effect of outreach on **at-risk** patients?

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1. Does outreach improve engagement?

Identification strategy:

- Reminder policy:
 - Each day: 1-3 reminders
- Outreach policy:
 - Day 1 of non-verification:
 - Sponsor message
 - Day 2 of non-verification:
 - Sponsor message
 - Day 3 of non-verification:
 - Refer to health worker
- Reality:

1. Does outreach improve engagement?

Identification strategy:

- Reminder policy:

Each day: 1-3 reminders

- Reality:

~ 30% of non-verifiers contacted each day.

- Outreach policy:

Day 1 of non-verification:

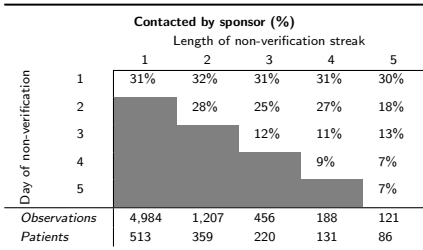
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Sponsor message

Day 2 of non-verification:

Sponsor message

Day 3 of non-verification:

Refer to health worker

- Reality:

~ 40% of non-verifiers not contacted at all.

		Total sponsor count instances (%)				
		Length of non-verification streak				
		1	2	3	4	5
Sum of messages	0	69%	44%	40%	39%	39%
	1	31%	53%	52%	46%	48%
	2		3%	8%	14%	12%
	3			0%	1%	1%
	4				0%	0%
	5					0%
Observations		4,984	1,207	456	188	121
Patients		513	359	220	131	86

1. Does outreach improve engagement?

Identification strategy:

- Reminder policy:

Each day: 1-3 reminders

- Reality:

~ 50% contacted on first two days.

- Outreach policy:

Day 1 of non-verification:

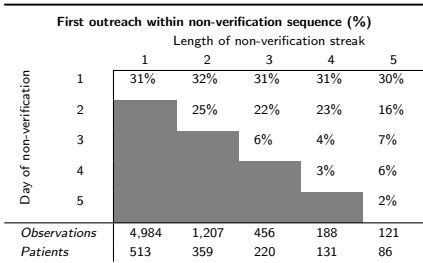
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1. Does outreach improve engagement?

Identification strategy:

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Each day: 1-3 reminders

- Reality:

Capacity issue?

- Outreach policy:

Day 1 of non-verification:

Sponsor message

Day 2 of non-verification:

Sponsor message

Day 3 of non-verification:

Refer to health worker

Calendar day averages

	Mean
Number of active patients	260
Number of non-verifiers	97
Number of contacts made	24

1. Does outreach improve engagement?

Identification strategy:

$$\underbrace{\text{clogit}(\text{Future_Verifier}_{i,t})}_{\substack{1. \text{ Next day verification} \\ 2. \text{ Next week verification}}} = \beta \underbrace{\text{Sponsor_Contact}_{i,t}}_{\text{Impact of outreach}} + \gamma_i \underbrace{\text{Patient}_i}_{\substack{\text{Patient} \\ \text{FE}}} + \underbrace{\lambda_{i,t} \mathbf{X}_{i,t}}_{\substack{\text{Controls:} \\ - \text{ Weekday} \\ - \text{ Reminders} \\ - \text{ Previous day} \\ \text{and week} \\ \text{verification}}} + \underbrace{\epsilon_{i,t}}_{\substack{\text{Errors} \\ \text{clustered} \\ \text{by patient}}}$$

- *Conditional Logistic Regression* to absorb patient FEs
- 63,907 patient-day observations (77%)
- 453 unique patients (76%)

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1. Does outreach improve engagement?

	Next_Week_Verifier (1)	Next_Day_Verifier (2)
Sponsor_Contact	1.326*** (0.067)	1.362*** (0.062)
Last_Week_Verifier	2.566*** (0.171)	2.509*** (0.120)
Last_Day_Verifier	2.432*** (0.099)	2.287*** (0.091)
Days_On_Platform	0.996*** (0.001)	1.000 (0.001)
Weekdays	✓	✓
Number of Reminders	✓	✓
Observations	63,907	75,237
Pseudo R^2	0.13	0.10

Exponentiated coefficients; Standard errors in parentheses

* $p < .10$, ** $p < .05$, *** $p < .01$

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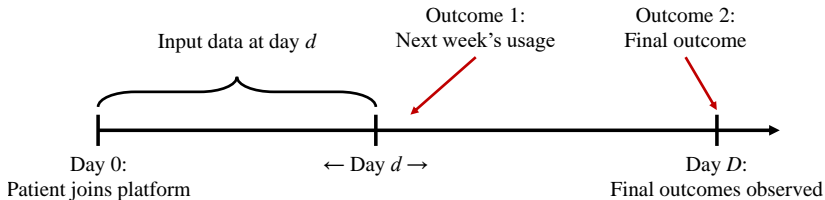
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2. Can we identify *at-risk* patients?

Framework



Features:

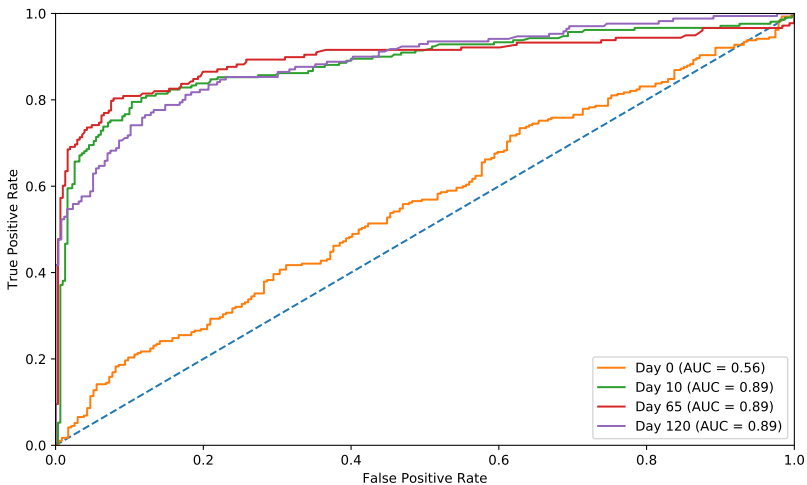
- Demographics
- Recent reminders
- Recent verification
- Recent messages
- Recent options accessed
- Time spent on platform
- Longest verification streak
- Longest non-verification streak

Outcomes:

- $Next_Week_Verifier_{i,t}$
- $Bad_Outcome_i$

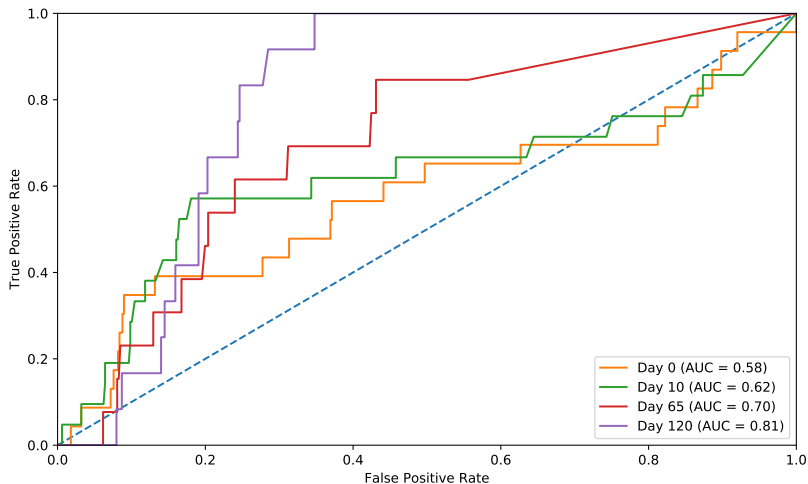
2. Can we identify *at-risk* patients?

Prediction outcome 1: $Next_Week_Verifier_{i,t}$



2. Can we identify *at-risk* patients?

Prediction outcome 2: Bad_Outcome_i



3. Does outreach work for *at-risk* patients?

Defining *at-risk* patients

- $At_Risk_{i,t} = 1$ if $Pred[Next_Week_Verifier_{i,t} = 0]$ and $Pred[Bad_Outcome_{i,t} = 1]$
- $Not_At_Risk_{i,t} = 1$ if $At_Risk_{i,t} = 0$

Identification strategy revisited:

$$\begin{aligned} \underbrace{clogit(Future_Verifier_{i,t})}_{\substack{1. \text{ Next day verification} \\ 2. \text{ Next week verification}}} &= \underbrace{\beta_1 Sponsor_Contact_{i,t} * At_Risk_{i,t}}_{\substack{\text{Impact of outreach} \\ \text{for } at_risk \text{ patients}}} \\ &+ \underbrace{\beta_2 Sponsor_Contact_{i,t} * Not_At_Risk_{i,t}}_{\substack{\text{Impact of outreach} \\ \text{for } not_at_risk \text{ patients}}} \\ &+ \underbrace{\gamma_i Patient_i}_{\substack{\text{Patient} \\ \text{FE}}} + \underbrace{\lambda_{i,t} \mathbf{X}_{i,t}}_{\substack{\text{Controls:} \\ - \text{ Weekday} \\ - \text{ Reminders} \\ - \text{ Previous day} \\ \text{and week} \\ \text{verification}}} + \underbrace{\epsilon_{i,t}}_{\substack{\text{Errors} \\ \text{clustered} \\ \text{by patient}}} \end{aligned}$$

3. Does outreach work for *at-risk* patients?

	Next_Week_Verifier (1)	Next_Week_Verifier (2)	Next_Day_Verifier (3)	Next_Day_Verifier (4)
Sponsor_Contact	1.285*** (0.088)		1.332*** (0.073)	
Sponsor_Contact * Not_At_Risk				
Sponsor_Contact * At_Risk				
Last_Week_Verifier	2.187*** (0.158)		2.224*** (0.120)	
Last_Day_Verifier	2.249*** (0.109)		2.125*** (0.100)	
Days_On_Platform	0.998 (0.002)		1.000 (0.001)	
Weekdays	✓		✓	
Number of Reminders	✓		✓	
Observations	33,867		47,748	
Pseudo R^2	0.088		0.074	

Exponentiated coefficients; Standard errors in parentheses

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Sponsor_Contact * Not_At_Risk		1.261*** (0.083)		1.335*** (0.071)
Sponsor_Contact * At_Risk		1.484** (0.291)		1.313* (0.211)
Last_Week_Verifier	2.187*** (0.158)	2.180*** (0.158)	2.224*** (0.120)	2.225*** (0.119)
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Post-Enrollment Managerial Implications

Sponsor outreach summary statistics (per calendar day)

- 14.5 patients contacted each day
 - 12.1 classified as *at-risk*
 - 2.4 classified as *not-at-risk*
- 68.8 *at-risk* patients **not** contacted

Takeaway

- ~ 16% of sponsor outreach is “misplaced”
- ~ 600 sponsor outreach instances should be re-prioritized

Conclusions and Next Steps

Objective

“Develop an implementable policy for personalization of treatment adherence support”

Pre-enrollment results

- Demographic data allows for *decent* ($AUC=0.76$) individual impact predictions
- Allows for initial assignment of treatment adherence support intensity

Post-enrollment results

- Does personal outreach improve engagement?
Yes, odds of next week verification increase by a factor of 1.3
- Can we identify *at-risk* patients?
Yes, using engagement info (at $d = 120$) we predict outcomes with $AUC=0.81$
Yes, using engagement info (at $d = 120$) we predict engagement with $AUC=0.89$
- Does personal outreach improve engagement of *at-risk* patients?
Yes, *at-risk* patients are as responsive to sponsor outreach as other patients

Future work

- Incorporate prediction accuracy into pre-enrollment recommendation
- Generate counterfactuals for post-enrollment recommendation
- RCTs to evaluate *personalized Keheala* interventions

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- Can we identify *at-risk* patients?
Yes, using engagement info (at $d = 120$) we predict outcomes with AUC=0.81
Yes, using engagement info (at $d = 120$) we predict engagement with AUC=0.89
- Does personal outreach improve engagement of *at-risk* patients?
Yes, *at-risk* patients are as responsive to sponsor outreach as other patients

Future work

- Incorporate prediction accuracy into pre-enrollment recommendation
- Generate counterfactuals for post-enrollment recommendation
- RCTs to evaluate *personalized Keheala* interventions

Demographic Features

	Experimental Condition			(p-value)
	Control (n=535)	Intervention (n=570)	All (n=1105)	
Female (%)	42.62	40.53	41.54	0.48
Age (yrs.)	31.87	30.63	31.23	0.09
Child (%)	9.533	7.895	8.688	0.33
English Language Preference (%)	60.56	68.25	64.52	0.01
Slum Dweller (%)	45.57	40.67	43.04	0.10
Number of Household Members	2.098	1.972	2.033	0.23
Education:				
None	18.46	13.01	15.64	0.01
Primary	33.52	30.05	31.73	0.22
Secondary	36.16	40.07	38.18	0.18
Advanced	11.86	16.87	14.45	0.02
Employment:				
Unemployed	25.61	22.89	24.20	0.29
Casual Day Worker	28.81	23.77	26.21	0.06
Self-Employed	23.16	26.58	24.93	0.19
Multiple Jobs	0.565	0.352	0.455	0.60
Formal Employment	17.70	21.13	19.47	0.15
Student	4.143	5.282	4.732	0.38
Travel Time to Clinic (minutes)	28.30	27.88	28.08	0.77
Smear-Positive (%)	55.85	61.01	58.50	0.10
Previously Treated (%)	65.85	68.49	67.21	0.35
HIV Coinfection (%)	32.82	28.49	30.59	0.12
Extrapulmonary (%)	23.22	23.33	23.28	0.97
Provided Nutrition Supplement (%)	92.18	90.46	91.28	0.32