

Operations Research Modeling in HIV Programs

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Partners AIDS Research Center
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Brigham and Women's Hospital

University of Washington Mini-Course in Operations Research
27 July 2007







-----Original Message-----

Sent: Thu 7/19/2007 8:24 PM

To: William Rodriguez

Subject: Urgent advice needed

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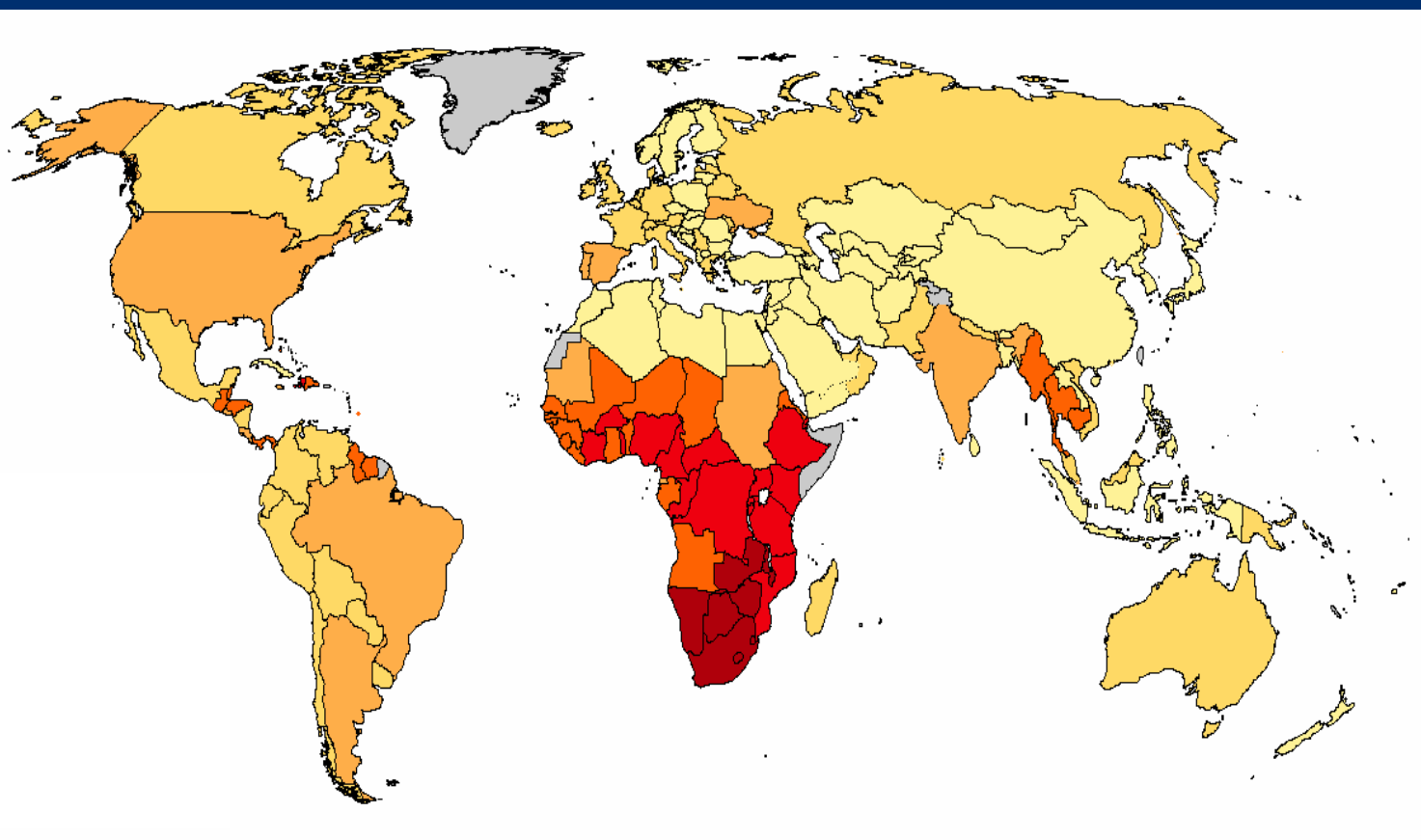
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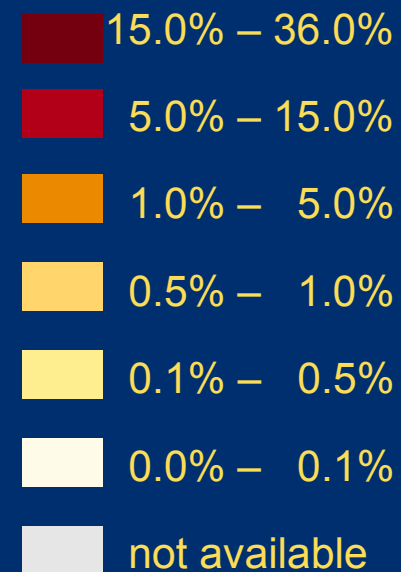
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Global HIV Update

40.4 million adults living with HIV/AIDS, December 2006

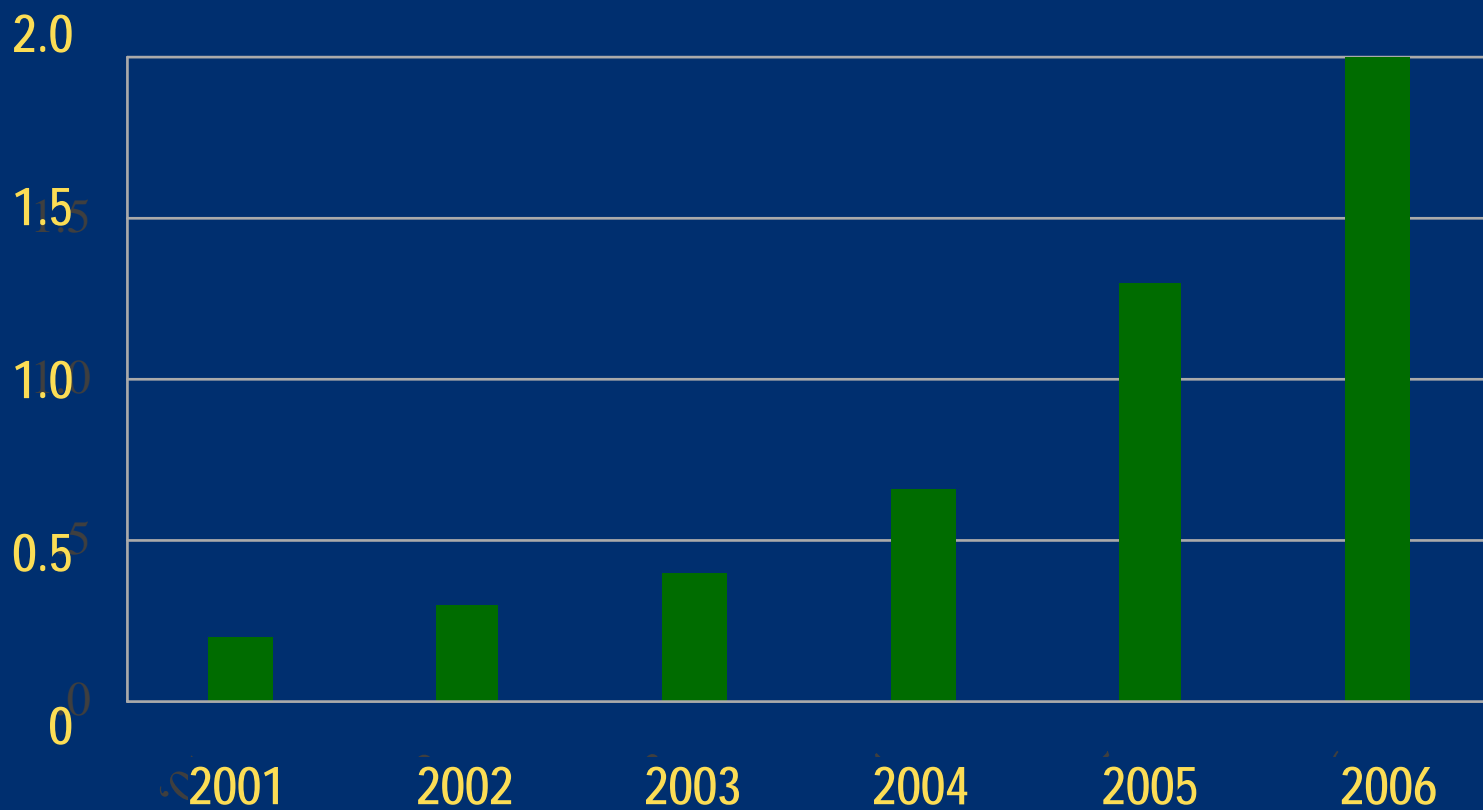


Adult prevalence rate

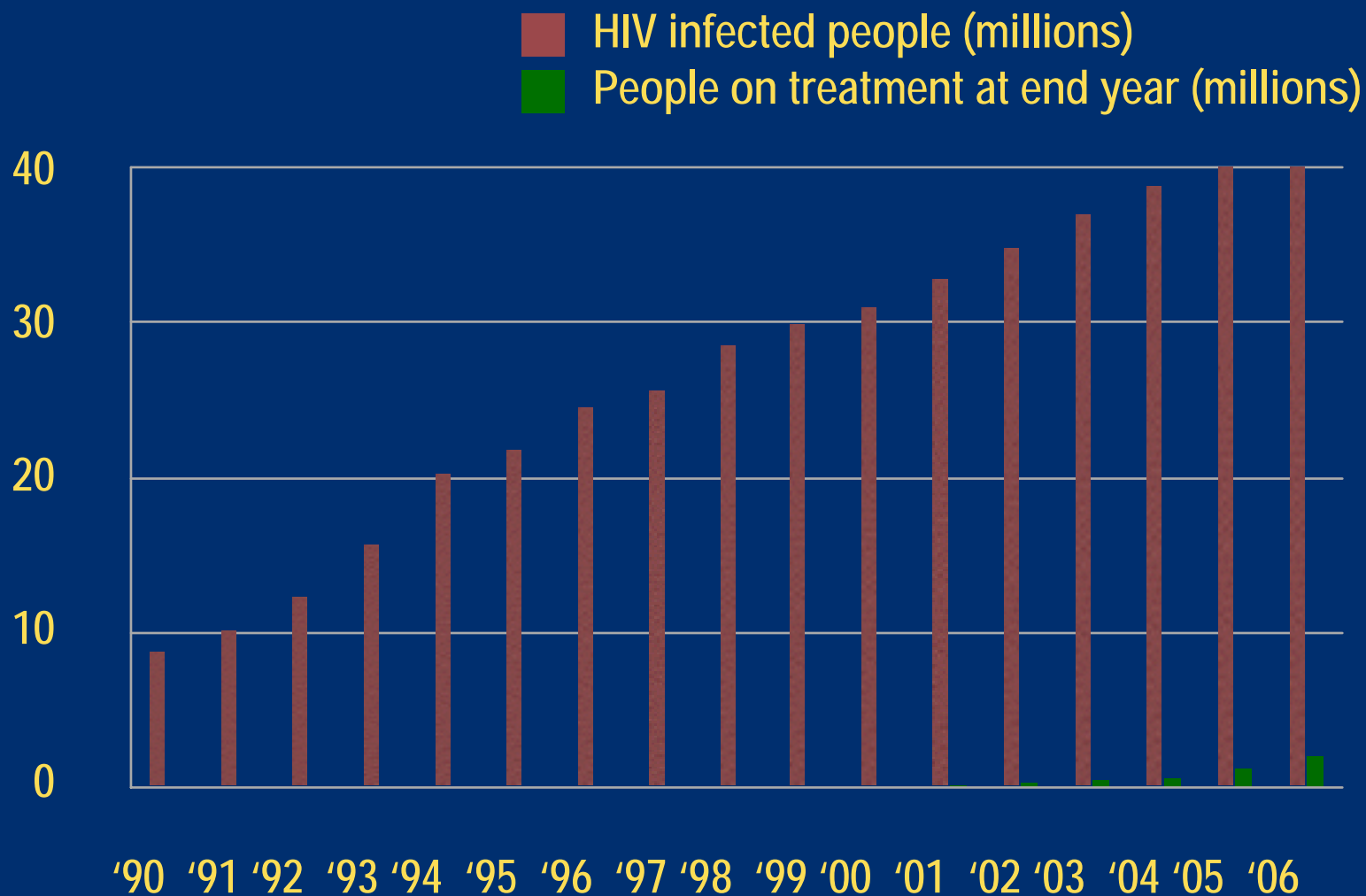


2.0 million people in low- and middle-income countries on ART

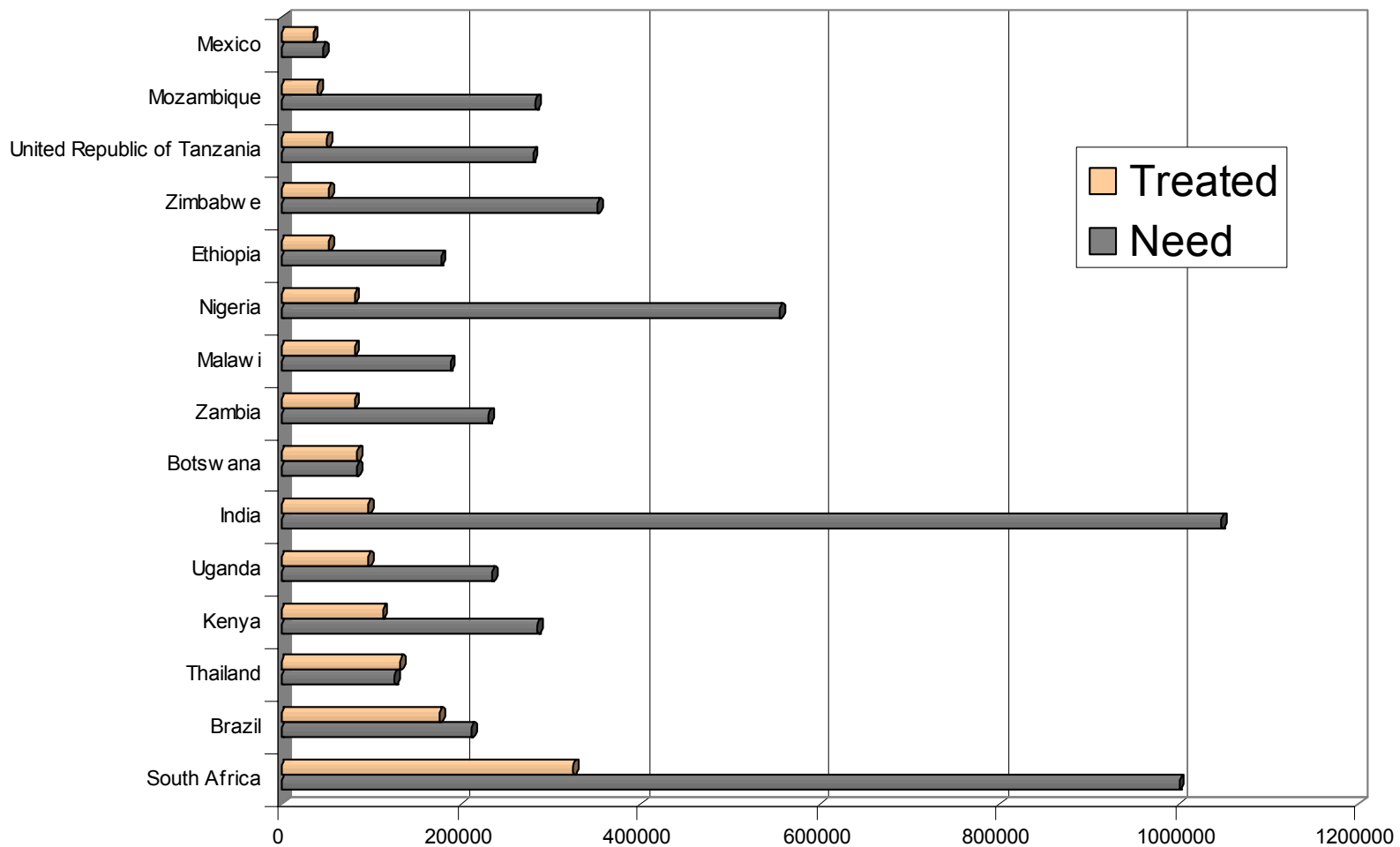
■ People on treatment at end year (millions)



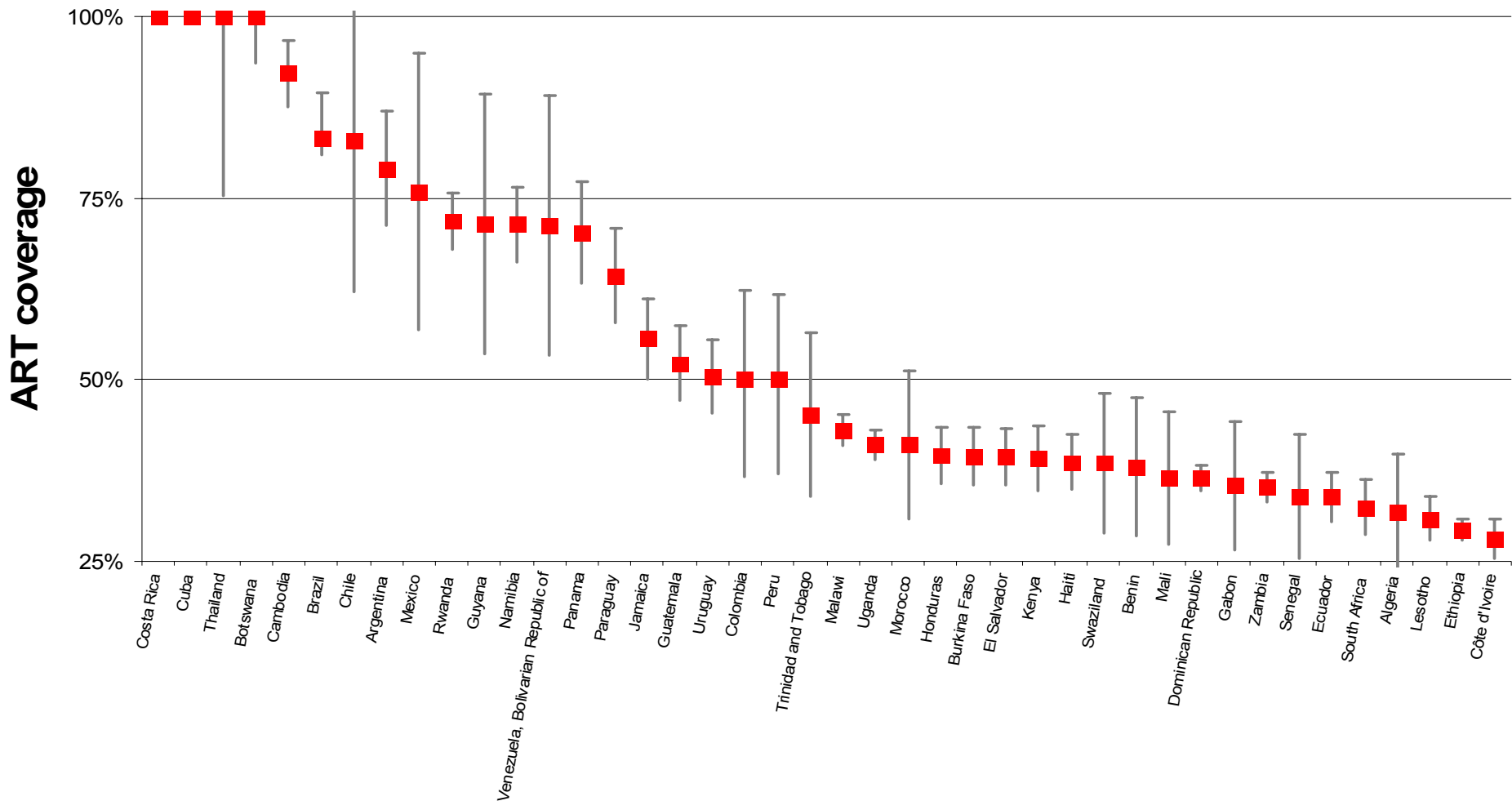
2.0 million people in low- and middle-income countries on ART



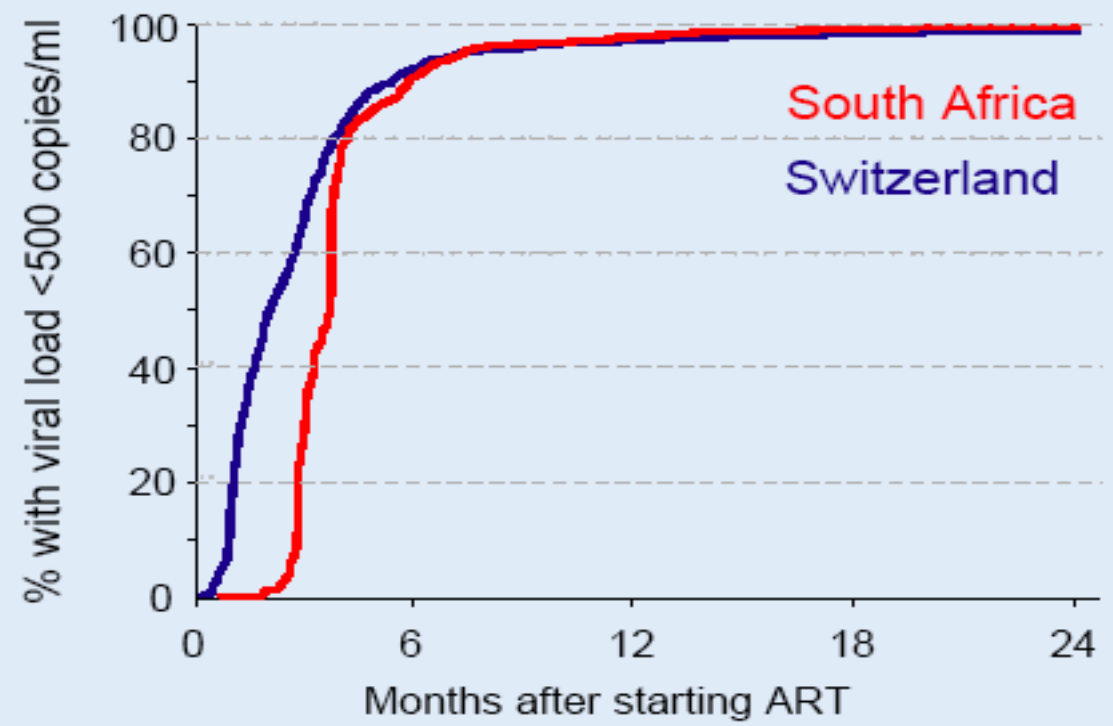
Low- and middle-income countries with the highest number of people receiving antiretroviral treatment, December 2006



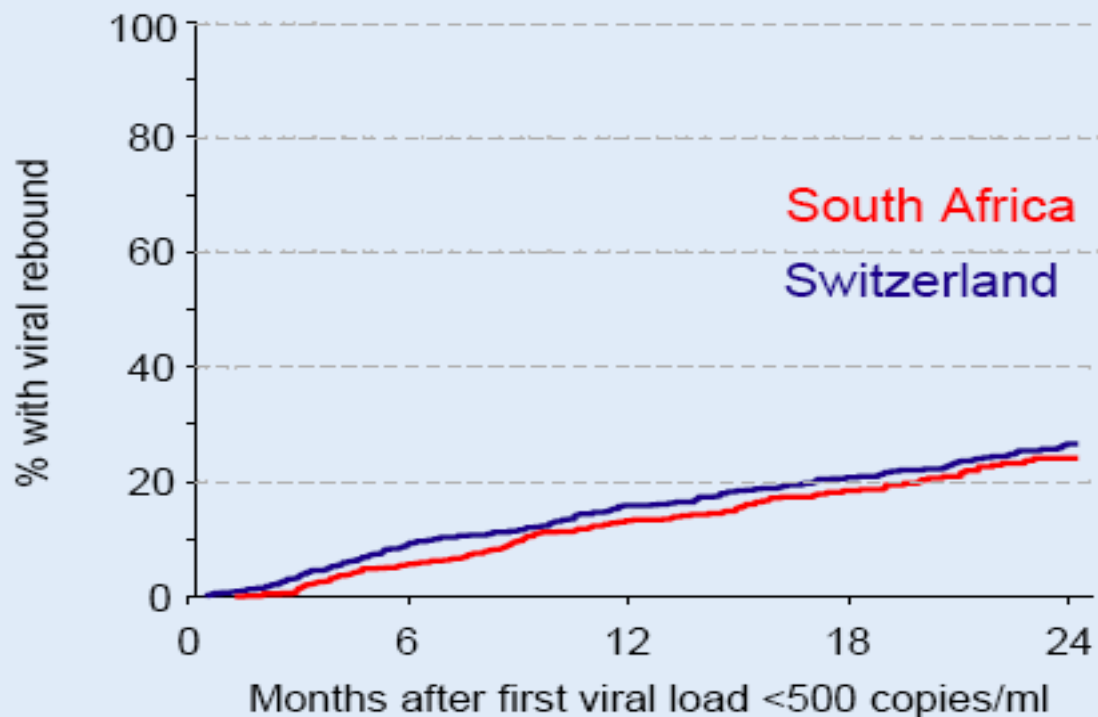
42 low- and middle-income countries had extended treatment to at least 28% of those in need as of December 2006



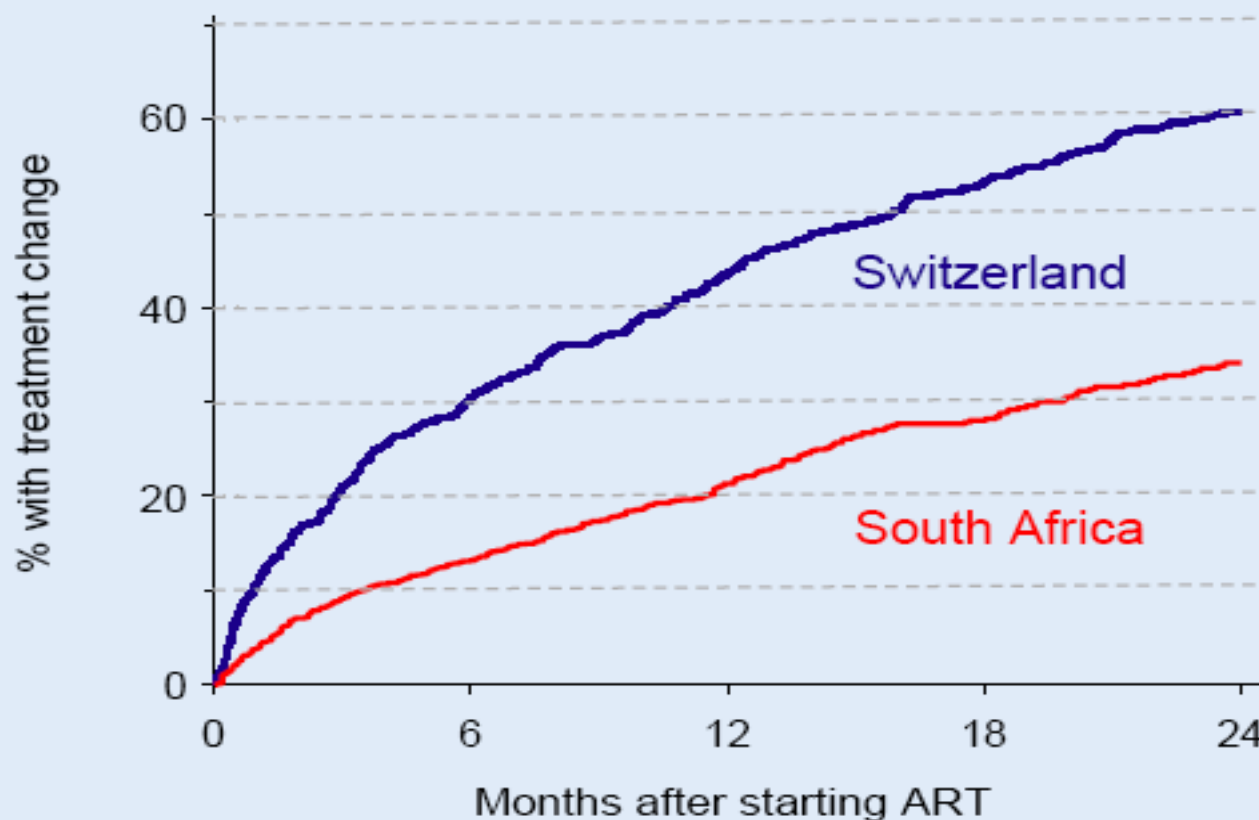
Initial virologic response (<500 copies/ml)



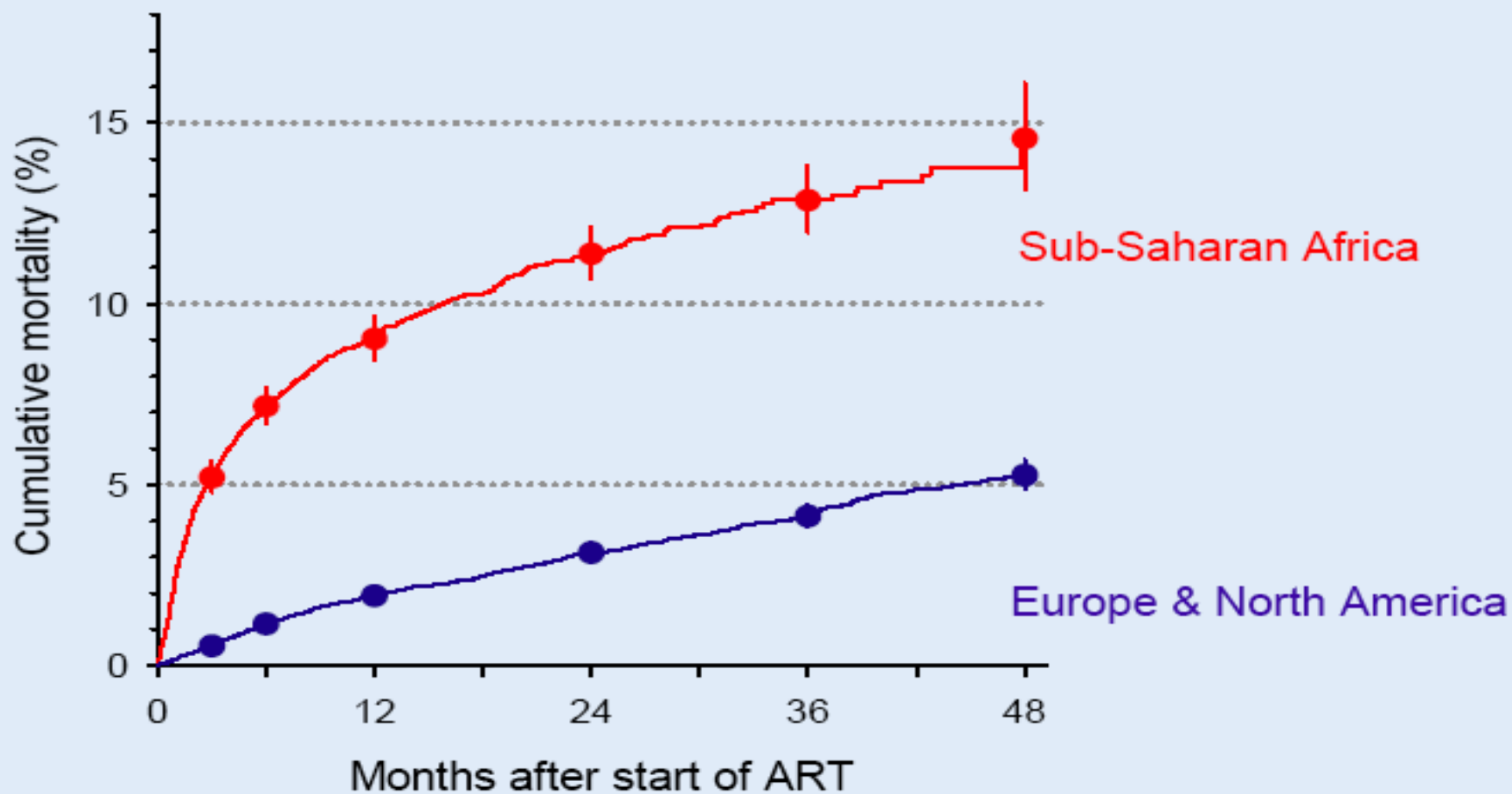
Viral rebound (≥ 500 copies/ml)



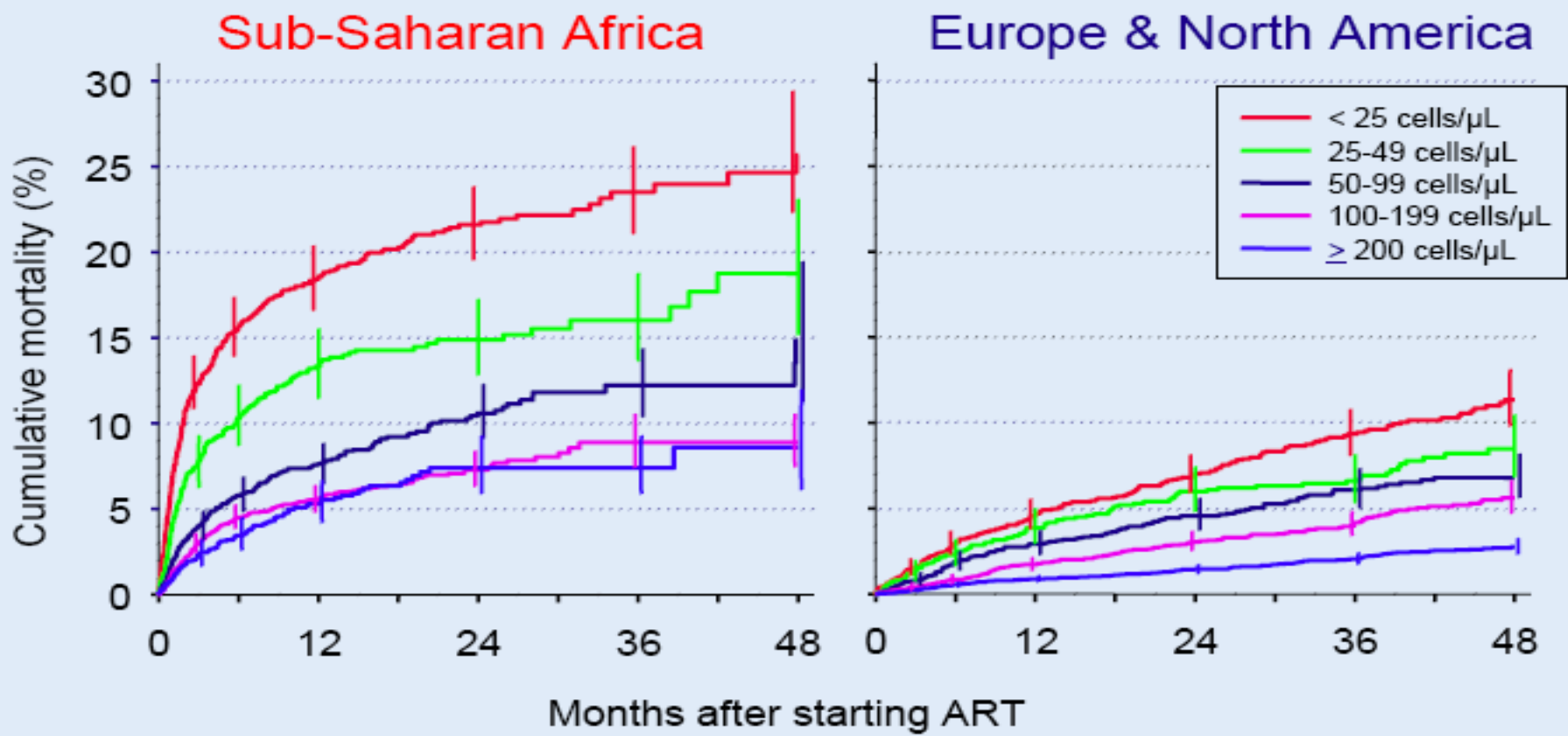
Treatment change (any change, including switching, substitution)



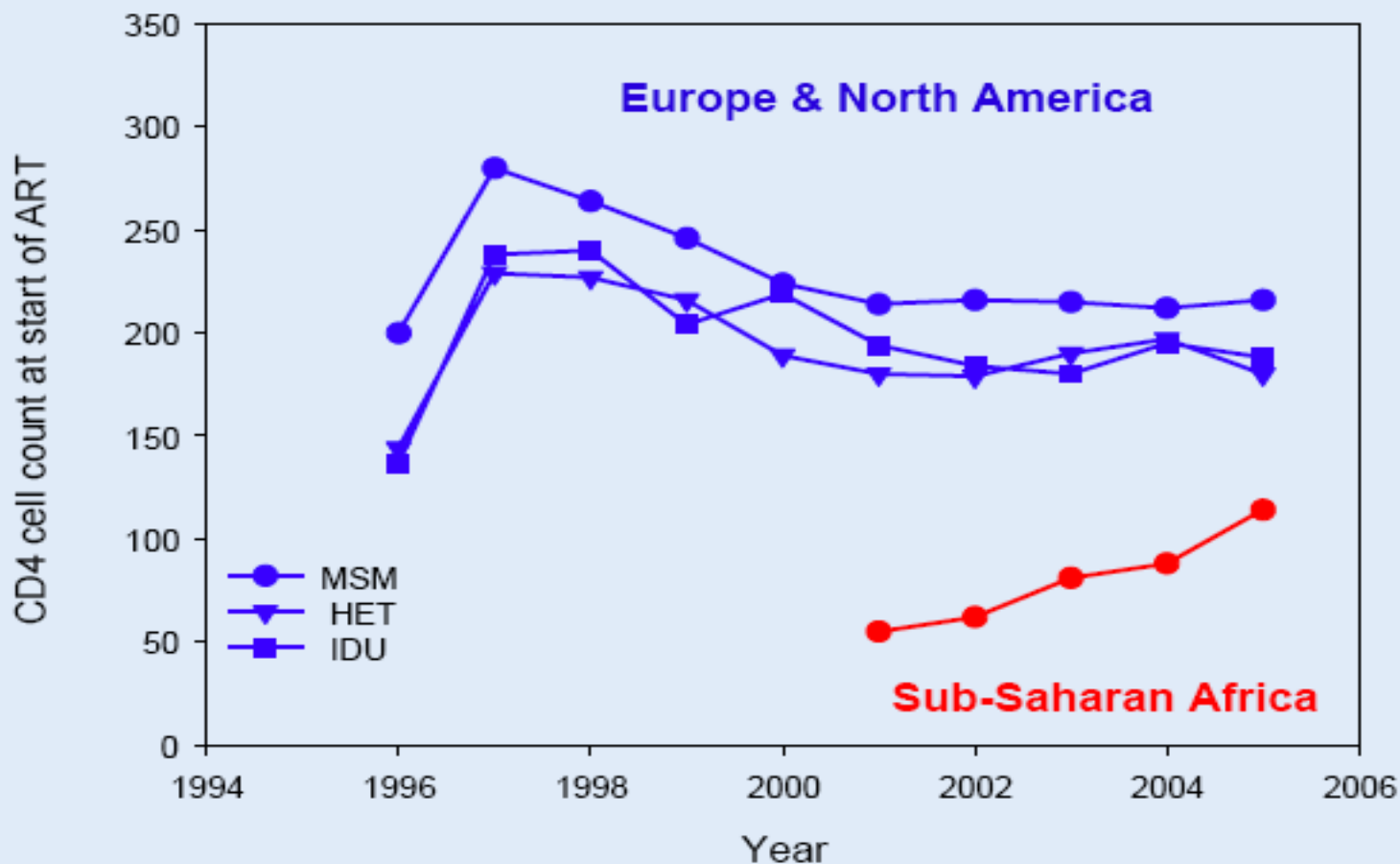
Mortality over four years



Mortality by baseline CD4 cell count



Median CD4 counts at start of ART Trends over time



Can we identify the factors that contribute to (or inhibit)
successful, rapid scale-up of HIV care?

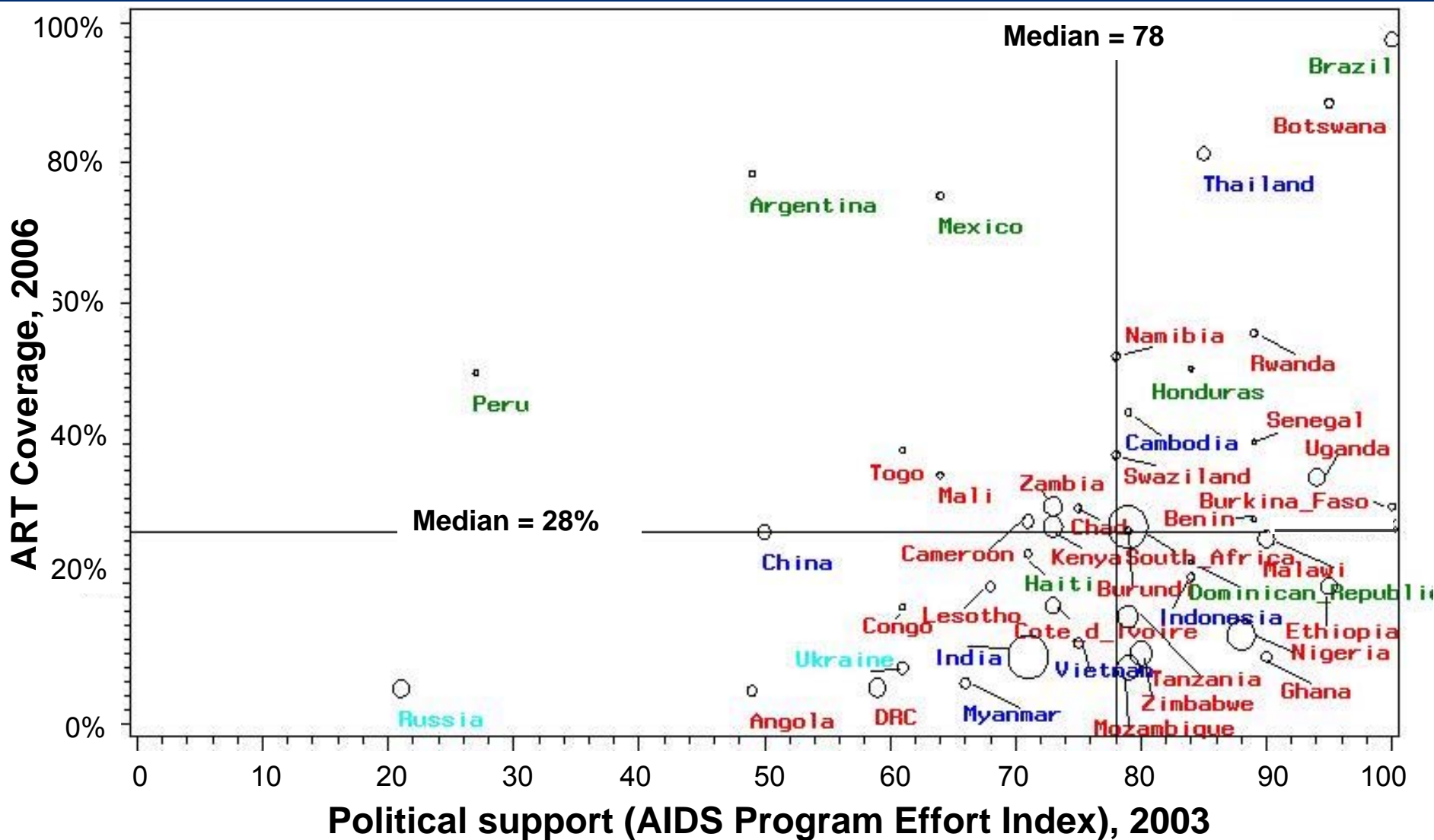
Problems, Constraints

- Poverty
- Hunger
- Gender inequality
- Conflict

Problems, Constraints

- Political will
- Funding
- Access to affordable medicines
- Infrastructure - Human Resources and physical capacity
- Health program management
- Laboratory systems and diagnostics
- Poverty
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ART Coverage and Political Will



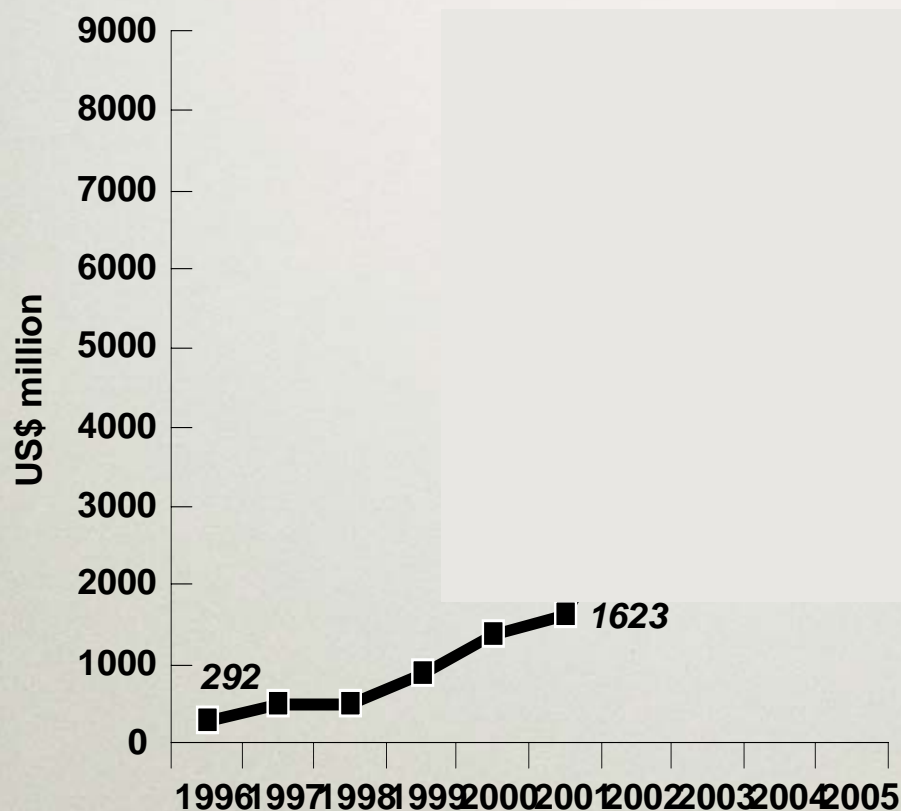
Note: Size of dot represents size of ART-eligible population per country

Red: Africa Blue: Asia Green: Latin America/Caribbean Teal: Eastern Europe

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Total global funding to cover AIDS-related expenditures, 1996-2005

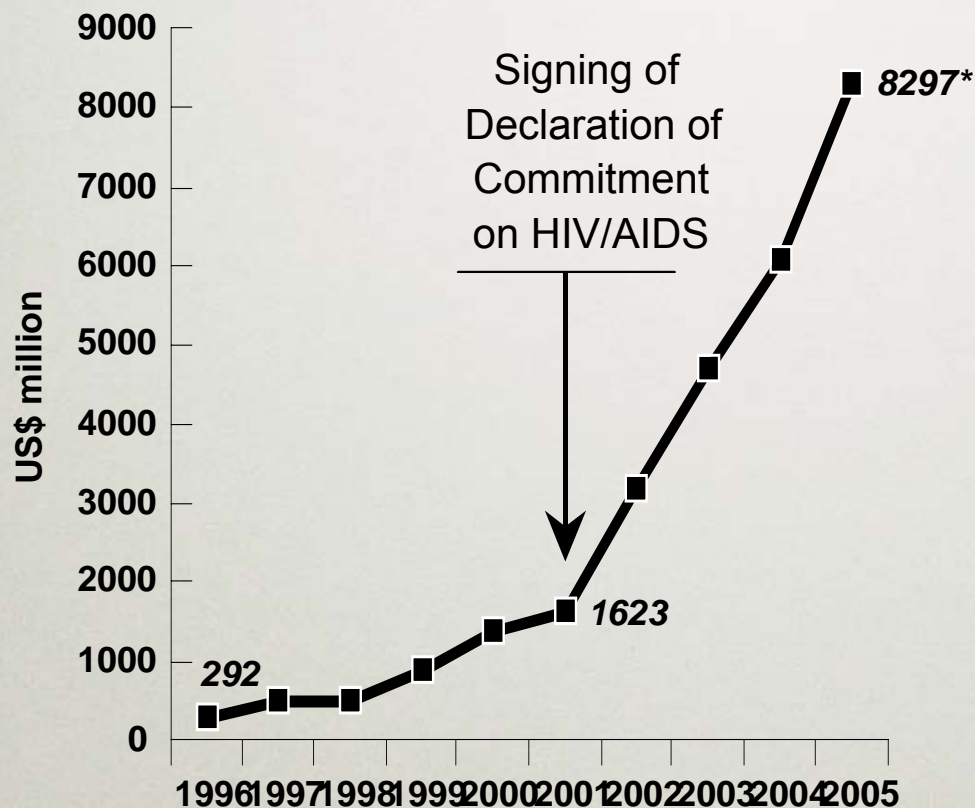


Data include:

- International donors, domestic spending (including public spending and out-of-pocket expenditures)
- International Foundations and Global Fund included from 2003 onwards, PEPFAR included from 2004 onwards

* Projections based on previous pledges and commitments (range of the estimation: US\$7.5 to US\$8.5 billion).

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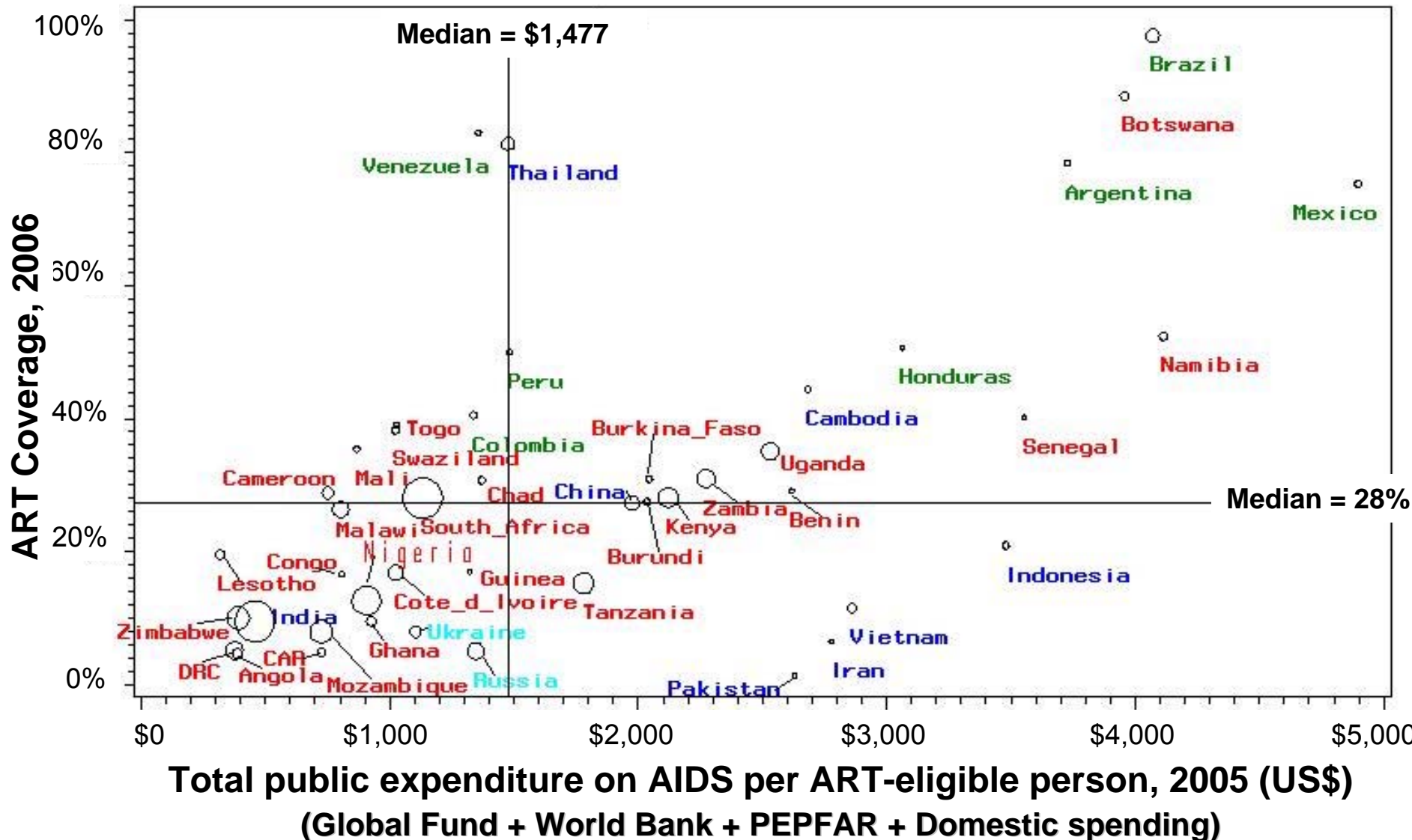


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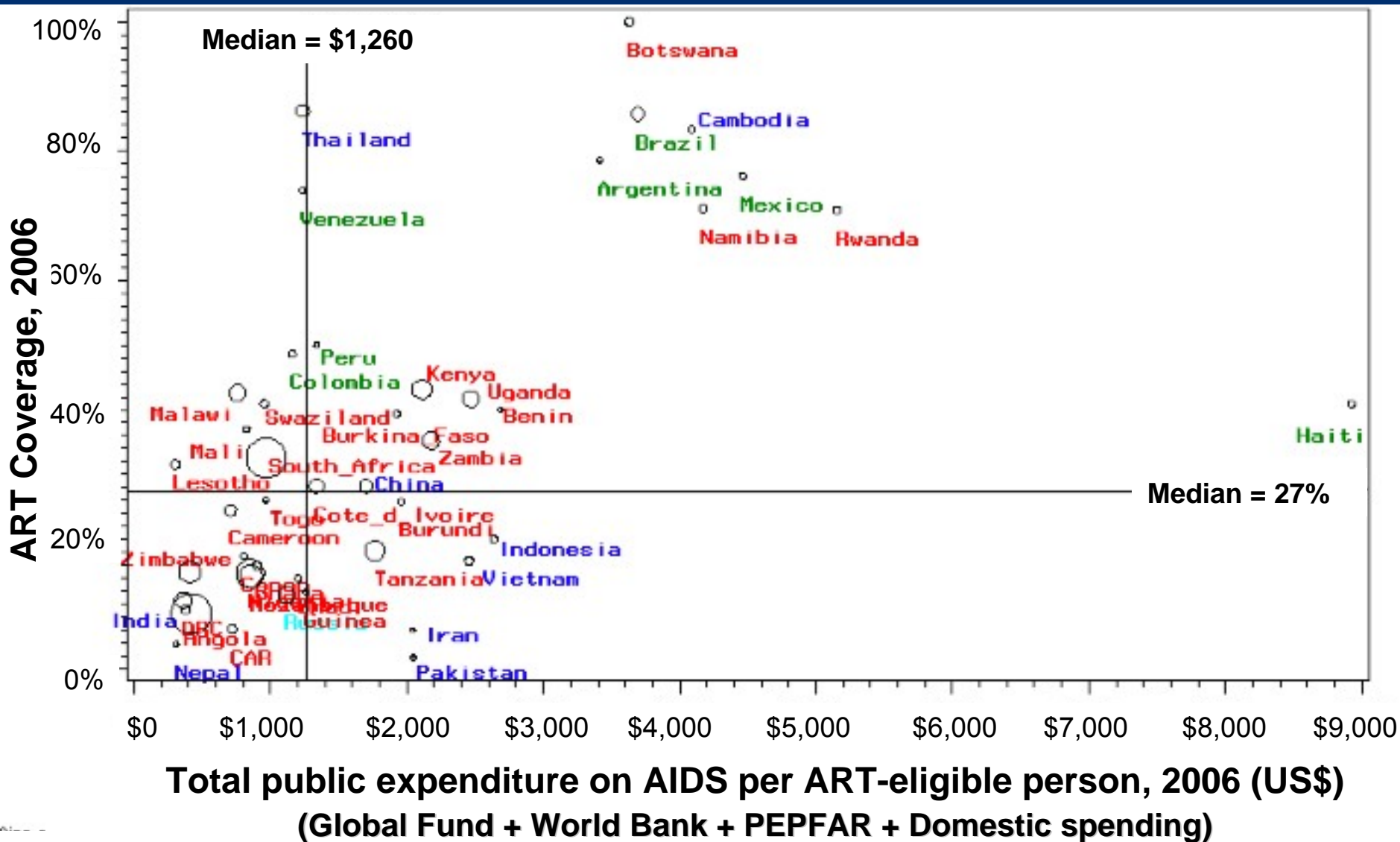
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ART Coverage and Total Expenditure for HIV/AIDS (2005)



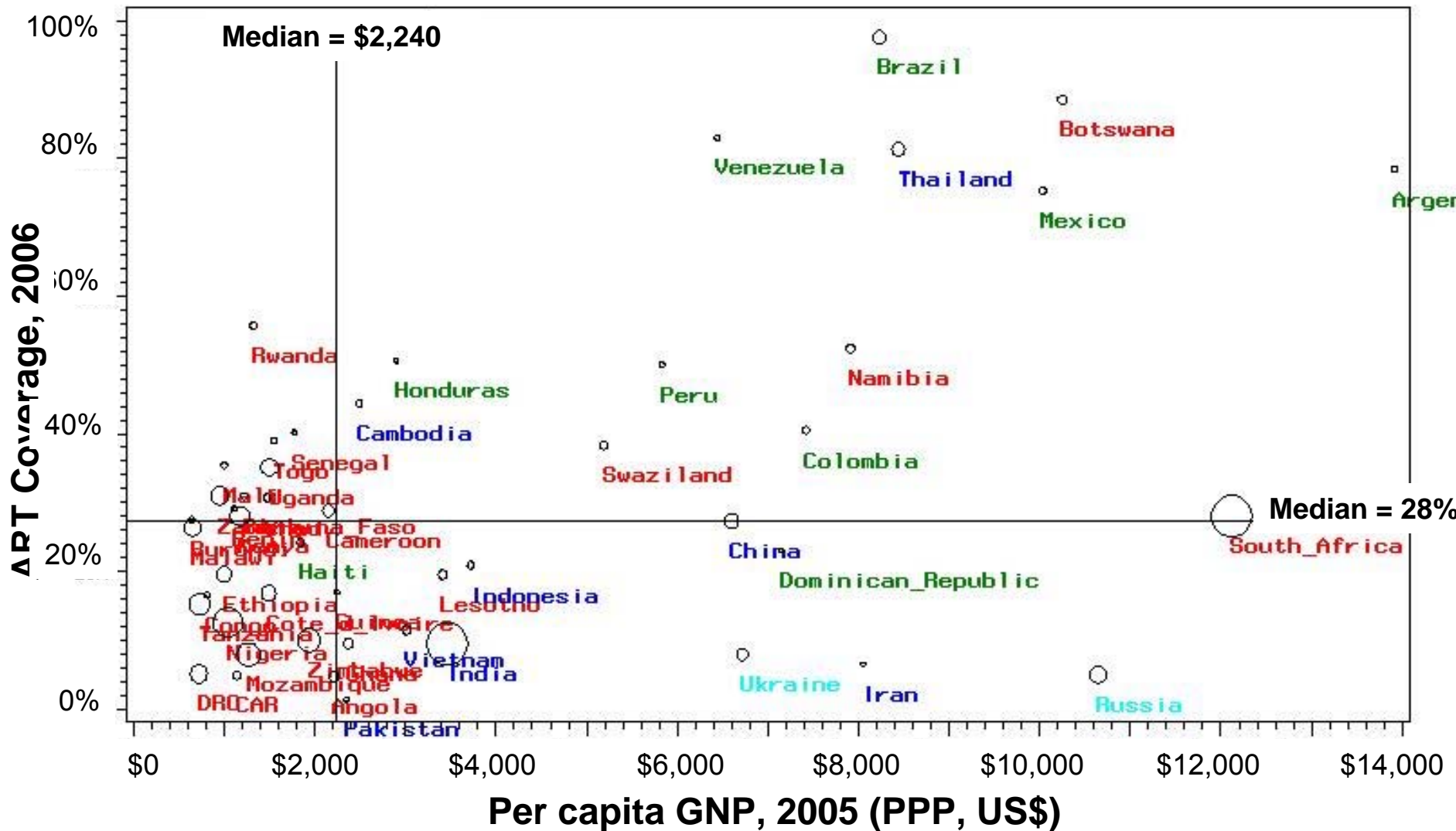
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ART Coverage and GNP



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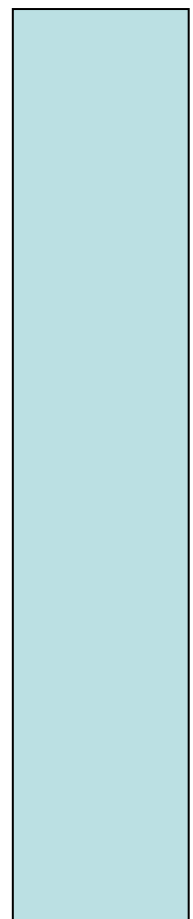
Problems, Constraints

- Political will
- Funding
- Access to affordable medicines
- Infrastructure - Human Resources and physical capacity
- Health program management
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- Poverty
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- Gender inequality
- Conflict

Medication Pricing: d4T(40) + 3TC + NVP

January 2004

\$4,400

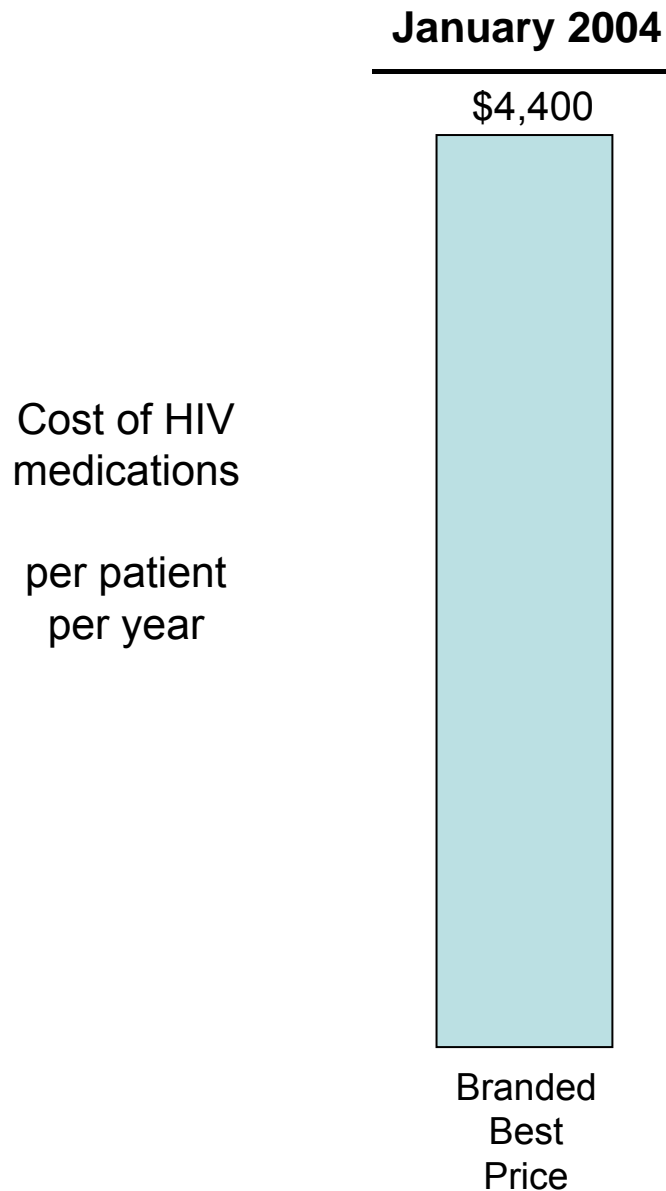


Cost of HIV
medications

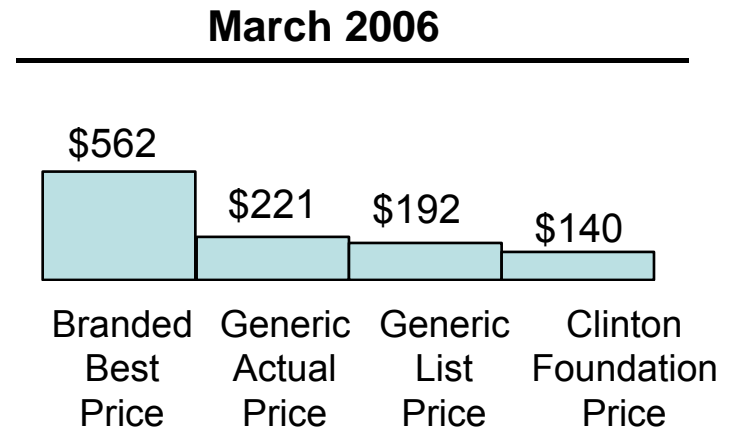
per patient
per year

Branded
Best
Price

Medication Pricing: d4T(40) + 3TC + NVP



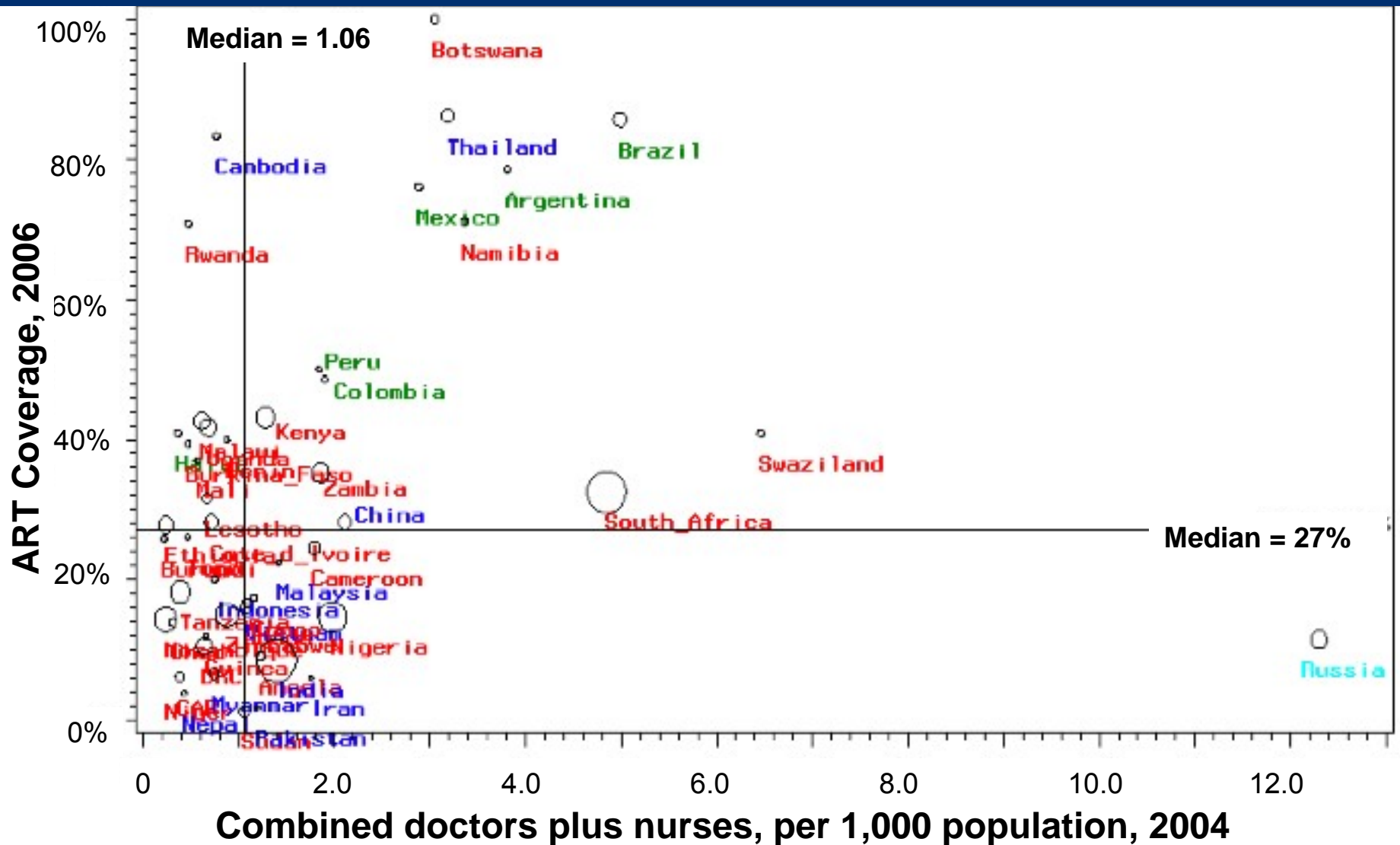
- Advocacy
- Generic suppliers
- Market-making (high-volume, low-margin market)



Problems, Constraints

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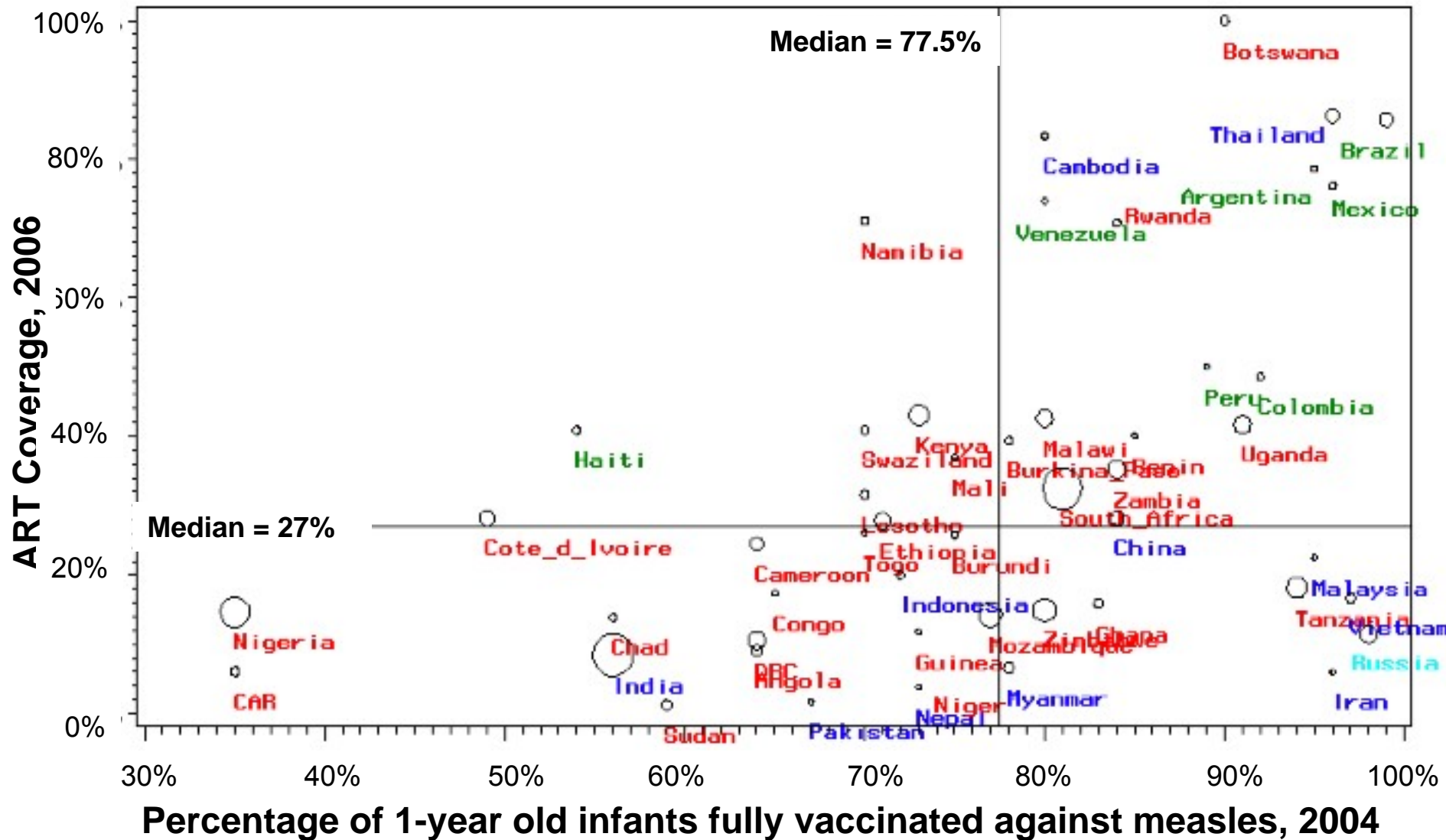
ART Coverage and Health Infrastructure



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HIV treatment program development

- **Phase 1: Start-up**
 - Goals: Begin treating people
 - Measures: # of clinics opened, # of patients on ART
 - Mode of Operation: Work with existing resources and structures

HIV treatment program development

- **Phase 2: Scale-up**
 - Goals: Treat target number of patients (some to all), provide effective care
 - Measures: # of clinics opened, # of patients on ART, clinical outcomes, costs
 - Mode of Operation: Short-term planning, use existing tools, learn as you go

HIV treatment program development

- **Phase 3: Sustained public health programs**
 - Goals: Provide effective care for all, build and sustain public health capacity
 - Measures: # of patients in care, clinical outcomes, impacts, costs, tradeoffs
 - Mode of Operation: New tools, long-term planning, sustainable financing

Classic OR

- How do you optimize X given constraint Y ?
- Examples of classic OR:
 - Designing the layout of a factory for efficient flow of materials
 - Scheduling airline traffic

$$\begin{aligned} \max f(X) &= \sum_{i=1}^n C_i X_i \\ \text{s.t. } \sum_{i=1}^n a_{i,j} X_i &\leq b, \quad i=1 \rightarrow n, j=1 \rightarrow m \end{aligned}$$

OR for HIV

- How do you optimize the number of patients in high-quality care given resource constraints?
 - Constraints may include human resources, lab capacity, money, space, etc.
- Goal of OR for HIV: provide decision makers with **support** to help them make informed decisions
- Clinton Foundation: use mathematical and operational models (and policy analyses) to provide **practical support for decision makers in public programs**

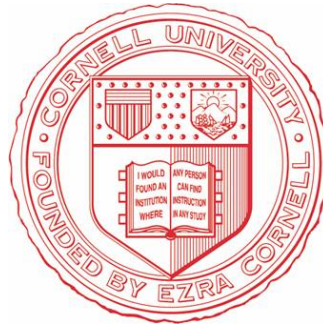
HIV OR Example

- If we opened a clinic tomorrow, and enrolled 15 patients each day, how many doctors will we need in April 2006?
- Or, if we plan to reach 100,000 patients in 2008, how many facilities, doctors, nurses, counselors, pharmacists, lab technicians do we need? How many of each commodity do we need?
- How do we assess trade-offs in *number in care* and *quality of care*? Or between investments in HIV and investments in control of other diseases?
- Resource planning
- Forecasting

Cornell University

Wei Xiong, PhD

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Acheson/Laibe Professor of Business Management and Leadership Studies
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Nathaniel Hupert, MD, MPH

Assistant Professor of Public Health and Medicine
Weill Cornell Medical College

CHAI Consortium for Strategic HIV Operations Research (CSHOR)

Ed Wood
CSHOR Program Director

Jessica Fast
Policy Analyst

Sandra Cress
Country Operations Director

Kate Waldman
Research Associate / Country Analyst

Meg O'Brien, PhD
Research Director

Adam Was
Country Analyst

Elizabeth McCarthy
Senior Policy Analyst

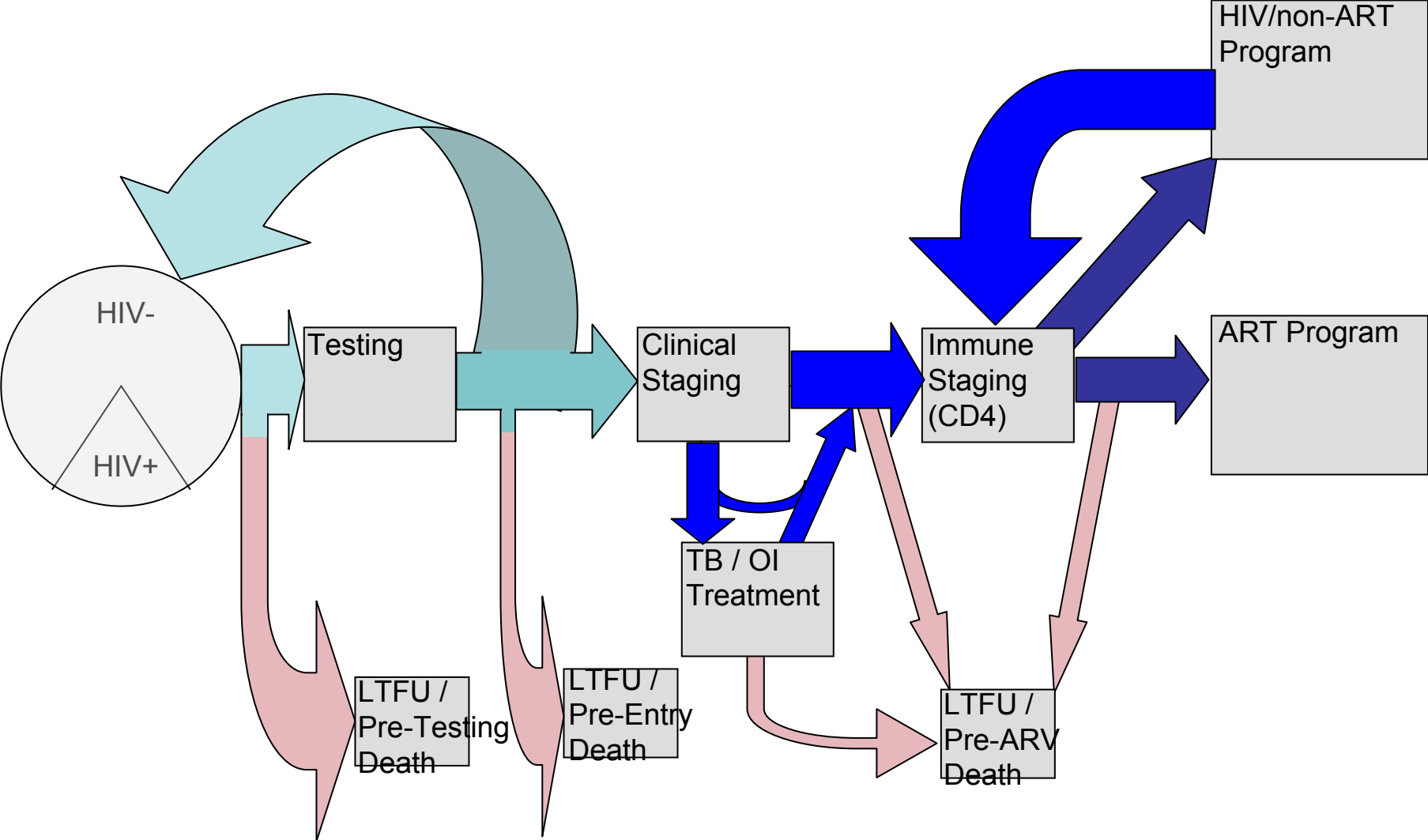
Alison Chick
Program Analyst



What is CSHOR?

- **Consortium for Strategic HIV Operations Research:** A division of the **Clinton Foundation HIV/AIDS Initiative (CHAI)** that assists governments in low- and middle-income countries to accelerate implementation of high-quality HIV care and treatment in the *most efficient and effective way possible*.
- **CSHOR activities:**
 - Development and application of decision support software to assist with resource planning
 - Policy analysis

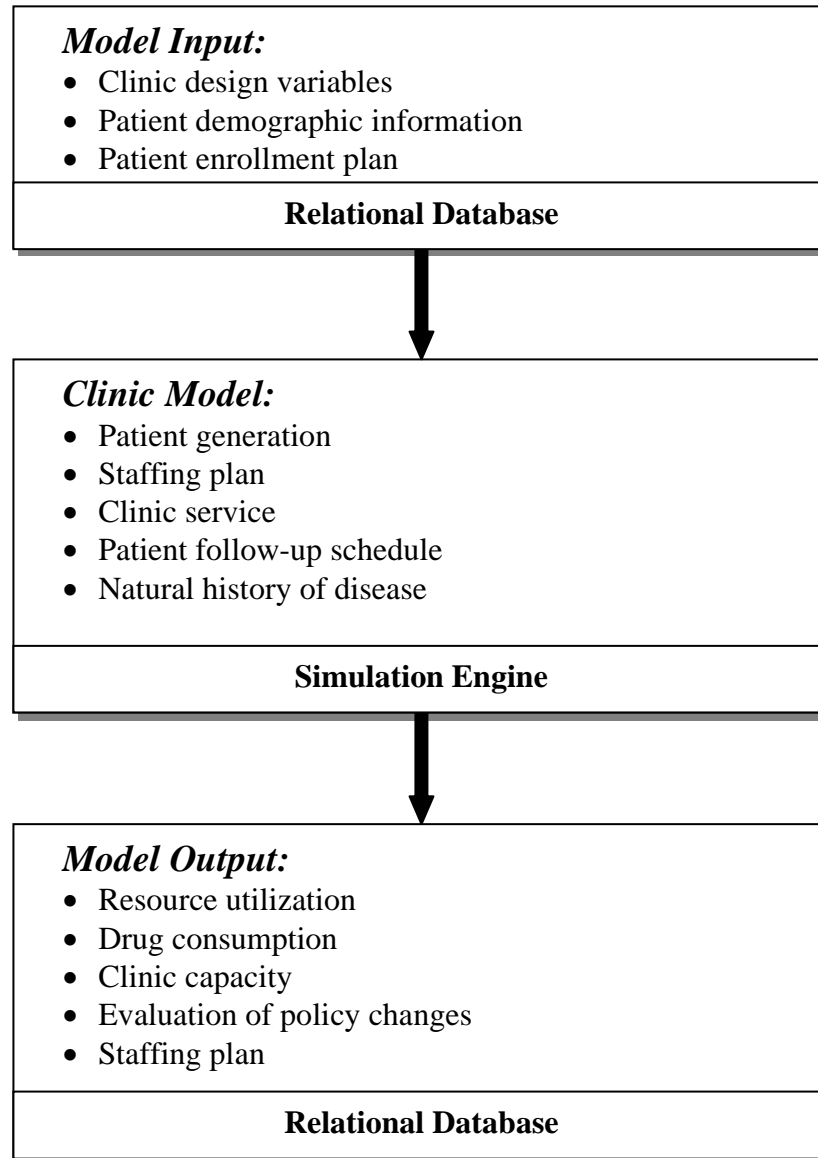
Initial modeling

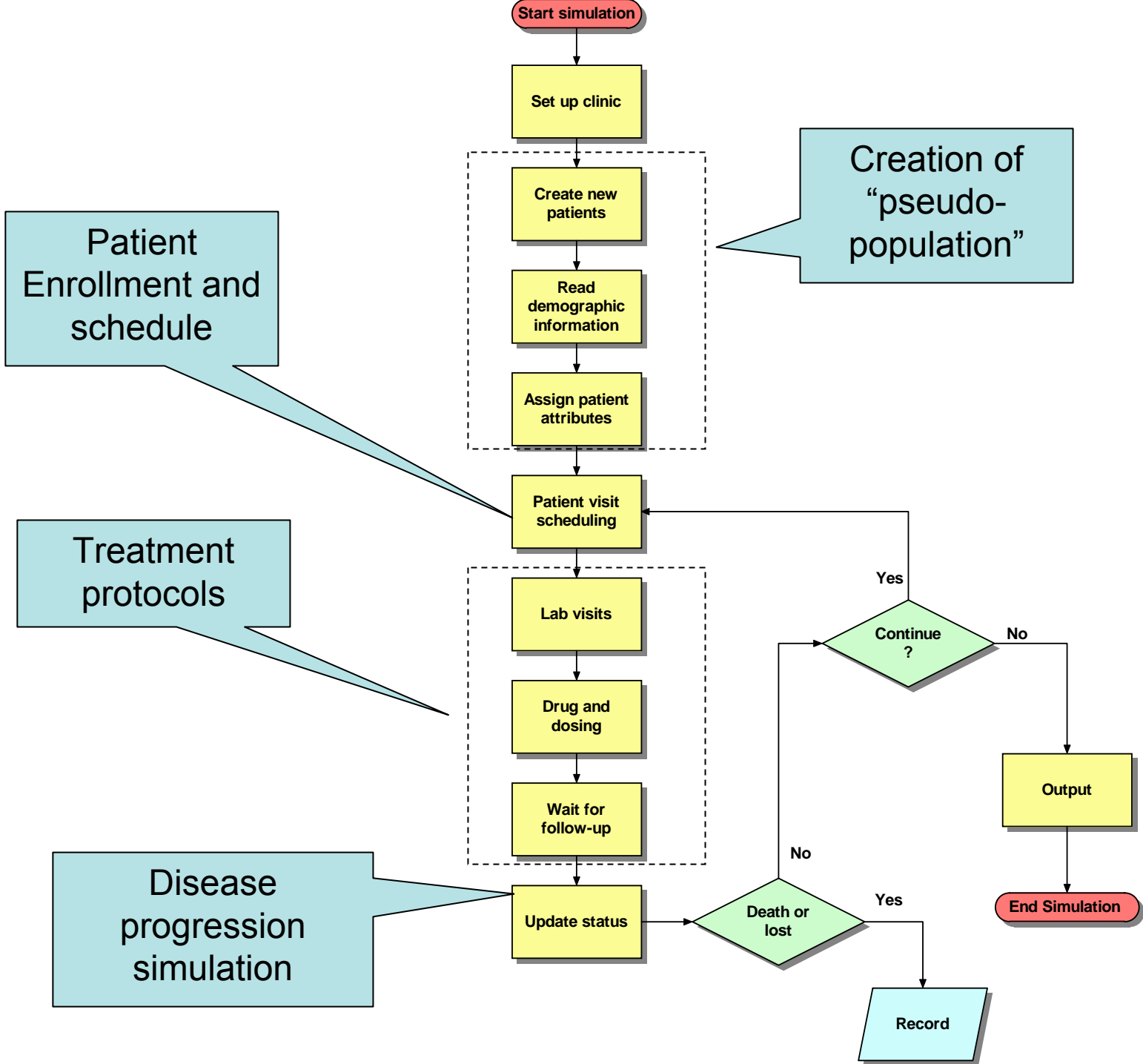


Model 1:

Simulation of an HIV clinic

- Simulation modeling of antiretroviral treatment clinics focusing on:
 - Human resource requirements
 - Pharmaceutical needs
 - Laboratory testing requirements





1. Create pseudo-population

- **Read demographic information from database (VBA)**
- **Assign random values to clinical attributes (VBA)**
 - Sex, Age
 - Pregnancy, Gestational age
 - WHO stage
 - CD4 count/percent
 - Viral load
 - Initial TB rate, Month of TB treatment
 - ARV experience, Number of weeks on ARV
 - Anemia
 - Weight
 - Peripheral neuropathy
 - Acute opportunistic infection
- **Create patients (VBA)**
- **Sent patients to the clinic according to the enrollment plan (ARENA)**

2. Enrollment and clinic services

- Enrollment plan
 - Weekly
 - Fixed number of enrollment
 - Ramp-up
 - Random distribution
- Clinic services
 - prescription
 - screening
 - counseling
 - testing

3. Treatment protocols

- Initial visit
- Follow-up visits
- Lab test
- Regimen

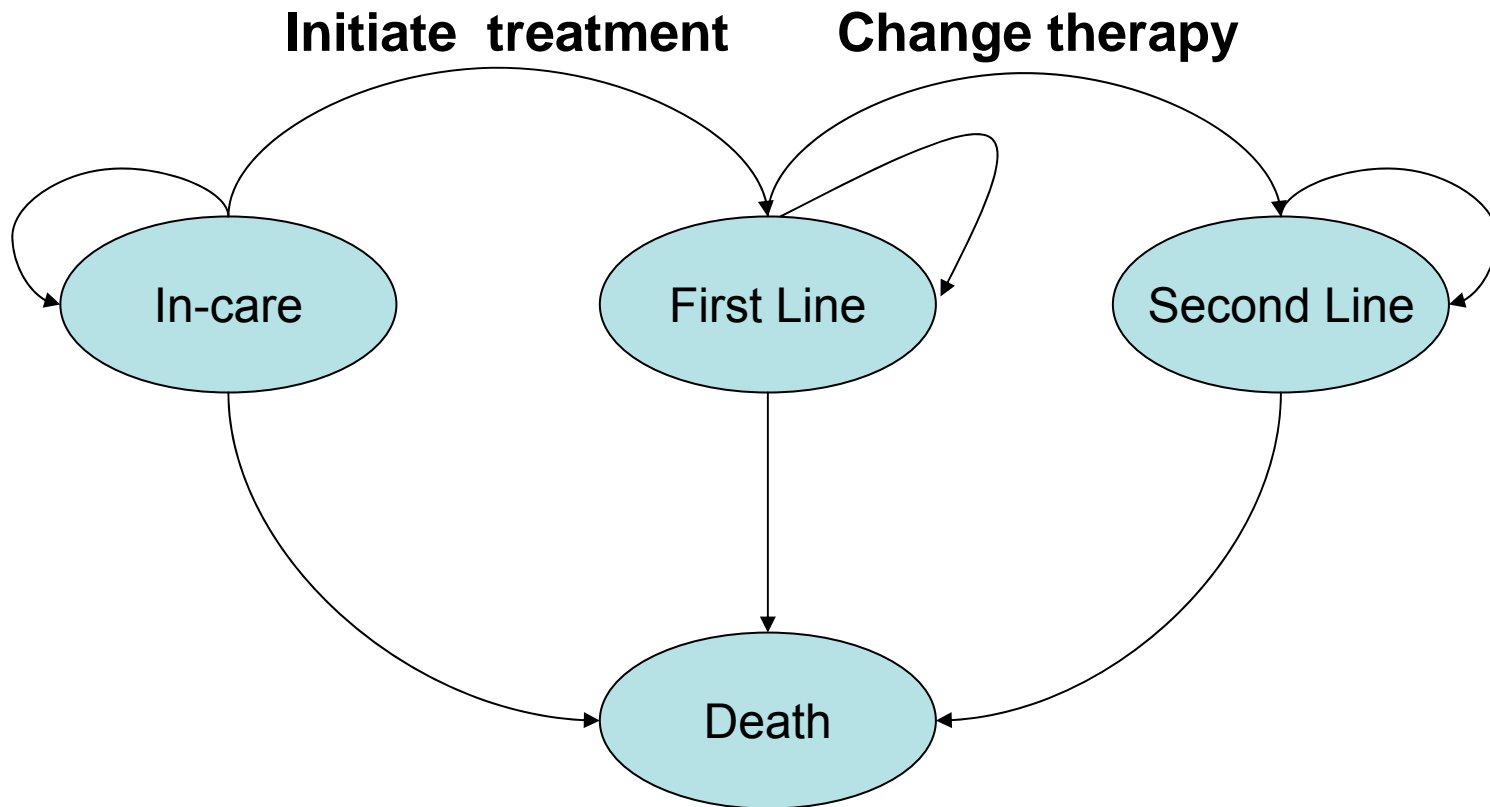
4. Disease progression

- Disease progression will dictate resource consumption
 - When to start a patient on treatment
 - When to switch therapy
 - Patient death
- Disease marker
 - CD4 count
 - Viral Load
 - WHO Clinical stage
 - Dead or alive

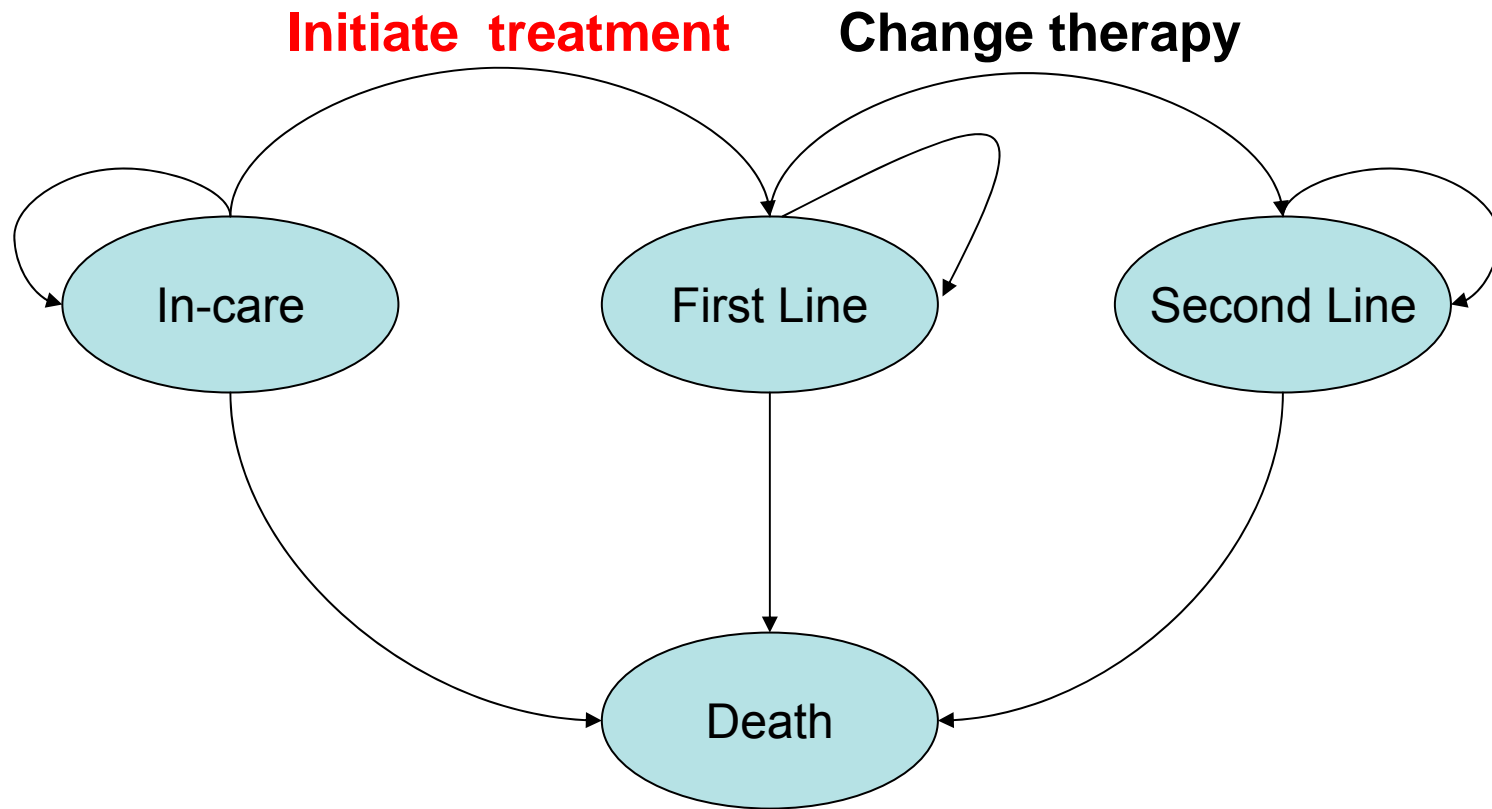
Disease Progression

- Start with given CD4+ count (%) in each VL category
- Determine time interval
- Adjust CD4+ count over that time interval (Mellors, et al., *Ann Int Med*, 1997)
- Viral load changes similarly
- WHO stage transition could be an input

Patient states related to resource consumption



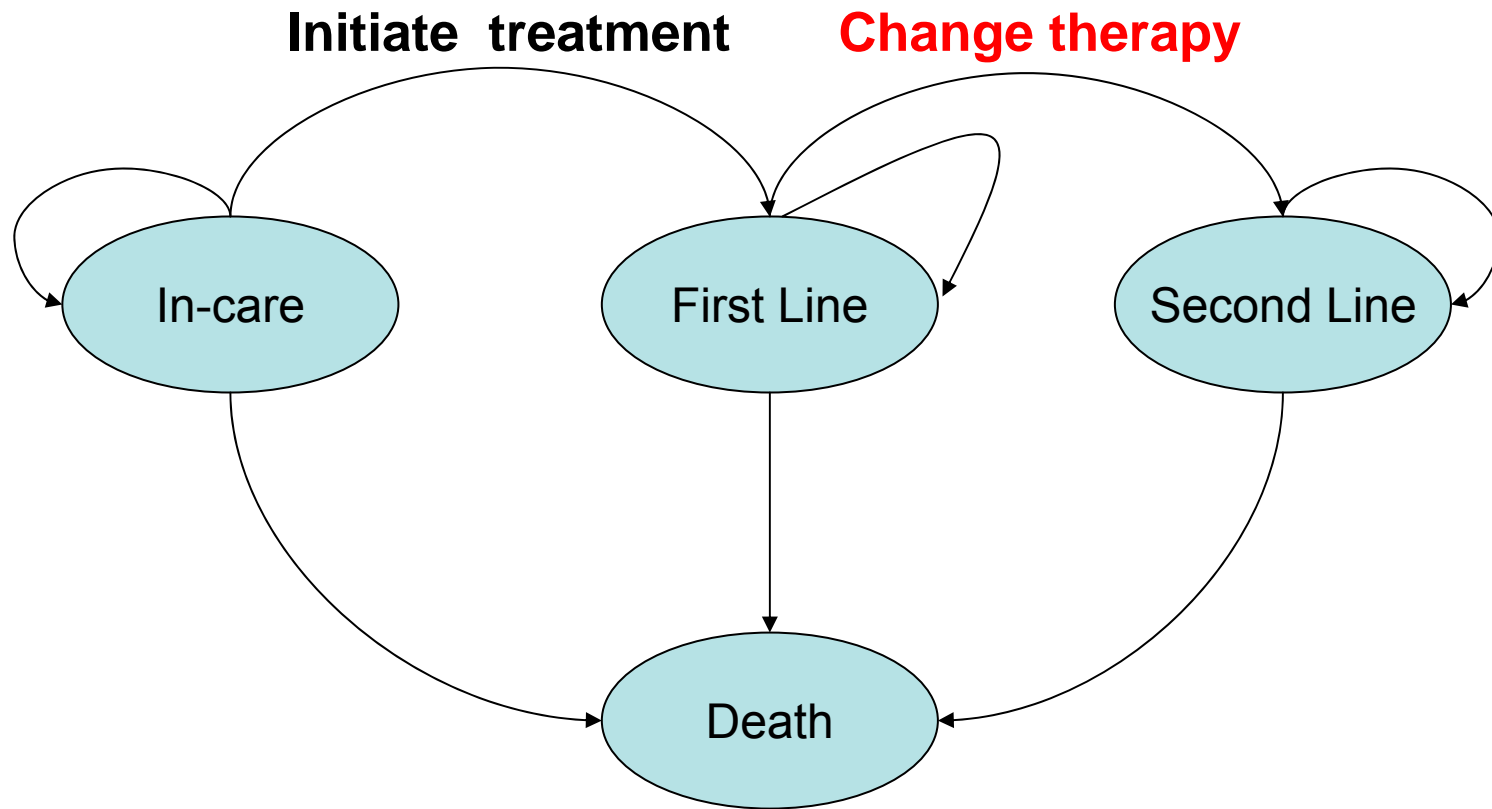
Patient states related to resource consumption



Treatment initiation

WHO CLINICAL STAGING	CD4 TESTING NOT AVAILABLE	CD4 TESTING AVAILABLE
1	Do not treat	Treat if CD4 count is below 200
2	Do not treat	Treat if CD4 count is below 200
3	Treat	Consider treatment if CD4 count < 350 and initiate ART before CD4 count < 200
4	Treat	Treat

Patient states related to resource consumption



When to change therapy?

Clinical failure ^a	New or recurrent WHO stage 4 condition ^{b,c}
CD4 cell failure ^d	<ul style="list-style-type: none">• Fall of CD4 count to pre-therapy baseline (or below); or• 50% fall from the on-treatment peak value (if known); or• persistent CD4 levels below 100 cells/mm^{3e}
Virological failure	Plasma viral load above 10 000 copies/ml ^f

--WHO ART Guidelines 2006

Other issues

- Single drug toxicity
- Opportunistic infections
- Patient death rate
- Patient loss-to-follow-up rate

Sample output:

OUTPUTS

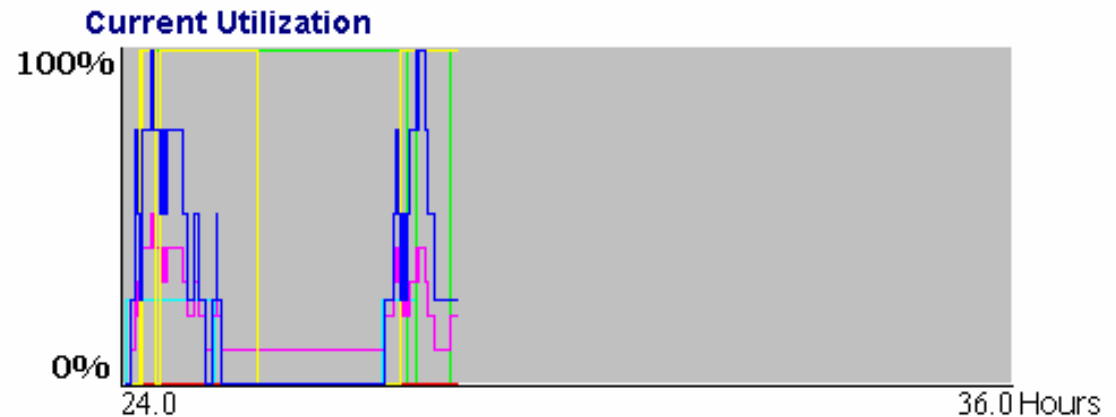
Simulation Day 2

Average Patient Throughput

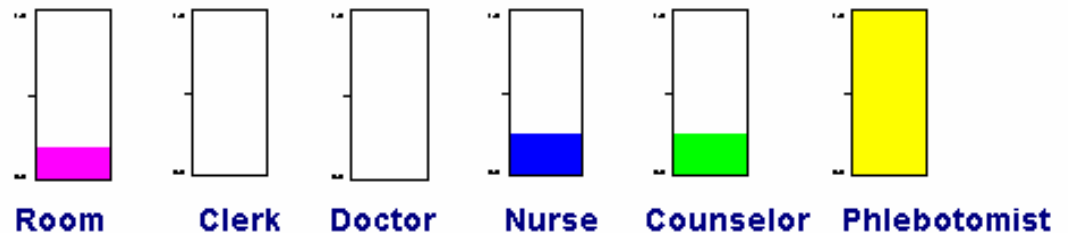
25.00 patients per day

Average Utilization %

Medical Staff			
Admissions	48	Phlebot.	118
Doctors	0	Counselors	137
Nurses	27	Rooms	25



Day 3



Forecast of demand for antiretroviral drugs in low and middle-income countries: 2007–2008

Omar Galárraga^a, Megan E. O'Brien^b, Juan Pablo Gutiérrez^{a,c},
 Françoise Renaud-Théry^d, Boniface Dongmo Nguimfack^d,
 Michel Beusenbergh^d, Katherine Waldman^b, Anil Soni^b,
 Stefano M. Bertozzi^{a,e,f} and Robert Greener^g

Background: Middle and low-income countries have scaled up HIV treatment in the past 5 years. To maintain this effort, information regarding the amounts and types of drugs is needed. Shortages or overstock of active pharmaceutical ingredients make the scale-up efforts more difficult and costly. To inform global planning and implementation, we estimate the volume of current and future demand for active pharmaceutical ingredients for first and second-line antiretroviral drugs.

Methods: Using regression analysis and documented assumptions, we estimated the number of individuals receiving antiretroviral drugs to 2008. The volume of active pharmaceutical ingredients was calculated using two methods: a normative approach modelling implementation of country-specific guidelines, and an empirical model projecting current trends in drug use estimated by a survey of country HIV programmes.

Results: The number of patients treated was estimated to reach 3.38 million by the end of 2008, of which 94.6% would be on first-line and 5.4% on second-line treatment. The largest estimated absolute demand volumes for 2008 were for nevirapine, lamivudine, and zidovudine using either approach; the largest proportional increases in 2007–2008, were observed for emtricitabine, tenofovir, didanosine, and nelfinavir. The gap between normative and empirical estimates was greatest (most positive) for tenofovir, zidovudine, didanosine, and smallest (most negative) for saquinavir and nelfinavir.

Conclusion: A comparison of the results from the normative and empirical demand quantities suggests that more tenofovir, zidovudine and didanosine would be required if national treatment guidelines were fully implemented, whereas the countries seem to be using more saquinavir and nelfinavir than would be required by their current guidelines.

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AIDS 2007, 21 (suppl 4):S97–S103

Keywords: anti-HIV agents/supply and distribution/*therapeutic use, antiretroviral therapy, developing countries: economics, forecasting/*demand, highly active/utlization

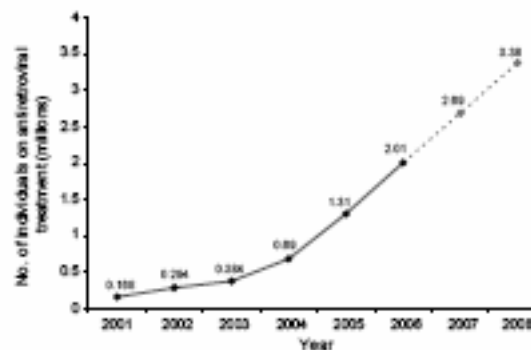


Fig. 1. Actual and predicted number of patients on treatment based on the scale-up observed in the past 12 months. ——— Reported data; - - - - forward projection.

Table 3. Estimated total individuals on antiretroviral therapy, by treatment type (in millions and percentage of total).

	2007	2008
First-line treatment	2.57	3.20
(% of total)	95.4	94.6
Second-line treatment	0.12	0.18
(% of total)	4.6	5.4
Total	2.69	3.38

Table 4. Volume of active pharmaceutical ingredient demand and differences by model (metric tons and percentage difference between models).

Drug	2007				2008			
	Normative	Empirical	Raw difference	% Difference	Normative	Empirical	Raw difference	% Difference
Stavudine	39	37	2	6	50	48	2	4
Lamivudine	250	218	31	14	316	267	50	19
Nevirapine	255	230	25	11	326	295	31	10
Zidovudine	173	104	69	67	221	104	117	113
Efavirenz	108	89	19	21	140	88	52	59
Didanosine	10	7	3	44	14	10	4	42
Tenofovir	4.7	1.3	3	277	10	1.9	8	482
Abacavir	14	23	-8	-36	21	30	-9	-30
Indinavir		0.5				0.8		
Saquinavir	0.01	1.2	-1	-99	0.01	1.7	-2	-100
Lopinavir	25	19	6	34	39	26	13	52
Nelfinavir	0.06	6	-6	-99	0.06	9.2	-9	-99
Atazanavir	1.2				1.4			
Emtricitabine	0.8				3.8			
Ritonavir	6.7				10			

Validation

- Validation will require pre- and post- assessments after analysis, creation of recommendations for enrollment and staffing plans, and implementation of those recommendations at a clinic or set of clinics in a resource-limited setting.
- This is very challenging from a data-collection point of view.

Model 2:

The lab facility location problem

- Decisions to make
 - Where to locate and how to size lab facilities
 - Which facility serves which clinic/hospital
 - How many lab tests should be done by each lab facility
- Issues drive the choice of facility locations.
 - cost reduction
 - demand allocation
 - equitable service supply
 - multiple lab services
 - blood sample keeping time, etc.

The lab facility location problem

- A set of *clinics* originates demand for lab services.
- The clinics' lab test demand must be satisfied by one or more *lab facilities*.
- Laboratories can be stand-alone facilities, or located within a clinic.
- Our goal is to minimize operating cost.
 - Given existing lab capacity, how should we allocate clinic demand among lab facilities.
 - If we are going to establish a central referral lab network in the future, we need to decide where to locate lab facilities.

Costs and Services

- Variable cost
 - Equipment
 - Vehicle
 - Fuel
 - Human resource
 - Lab technicians, drivers, and maintenance engineers
 - Lab consumables/Reagents
- Fixed cost
 - Facility construction/Rental
 - Human resource
 - Lab managers/administrators, clerks
 - Other overhead
- Service types, service times/capacities

Problem definition

- There are a set of lab facilities and a set of clinics requiring tests.
- In a given period, each lab has a capacity, and each site needs a number of tests to be done.
- Given the associated cost, we want to allocate tests to laboratory facilities in a way that minimizes costs.

Objective Function

$$\min z = \sum_{t \in T} \sum_{i \in I} \sum_{j \in J} x_{ijt} c_{ij} + \sum_{j \in J} f_j y_{jt}$$

x_{ijt} the fraction of clinic i 's lab test sent to lab facility j in period t

y_j the binary variable which is equal to 1 if lab facility j is open and to 0 otherwise

f_j the cost to establish a laboratory facility

c_{ij} the cost to both transport and test blood samples to lab j from a clinic site i

Constraints

$$\sum_{j \in J} x_{ijt} = 1, \quad \forall i \in I, t \in T$$

- demand constraints

$$\sum_{i \in I} x_{ij(t-t_{ij})} d_{i(t-t_{ij})} \leq s_j y_j, \quad \forall j \in J, t \in T$$

- capacity constraints

$$(t_{ij} - R)x_{ijt} \leq 0$$

- blood sample shelf life < R

Simulation

- Based on the results from the previous model, we can carry out a detailed analysis for each laboratory facility.
- Simulation can incorporate uncertainty into the model
 - Road status during rainy season
 - Reagent supply uncertainty
 - Machine down time



1. Country and Project

2. Enrollment Plan

3. Lab Schedules

4. Age Distribution

5. Attrition Rate

6. View Output

Start a New Laboratory Forecasting Project

Select a country

Select the **Country** in which the forecast takes place from the drop down menu. This will determine the default values of demographic data that will be used to make the forecast. (These defaults can be changed later.)

Input your project name

Enter a name for the forecast in the **Project** box.

Choose File

no file selected

Upload

If you have saved an input file on your local computer, you can click on the **Browse** to find the file and then click on the **Upload** button to upload your data. You can continue if there is no data to upload.



1. Country and Project

2. Enrollment Plan

3. Lab Schedules

4. Age Distribution

5. Attrition Rate

6. V

Historical and Planned Patient Enrollment

Enter the date that the clinic opened in the **Clinic Start Date** box.

Enter today's date under the **Today's Date** box.

Enter the *total* number of patients currently enrolled in the clinic in the **Total Enrollment Over This Period** box.

The date format is mm/dd/yyyy.

Clinic start date

Today's date

Total number of patients enrolled over this period

Enter the **Start Date of Forecast** and the **End Date of Forecast** in their respective boxes.

Enter the number of patients to be enrolled in the clinic *each week* in the **Weekly Enrollment During Forecast Period** box.

Start date of forecast

End date of forecast

Average Weekly enrollment during forecast period



- 1. Country and Project
- 2. Enrollment Plan
- 3. Lab Schedules
- 4. Age Distribution
- 5. Attrition Rate
- 6. View Output

Schedule for Patients ON ARVs

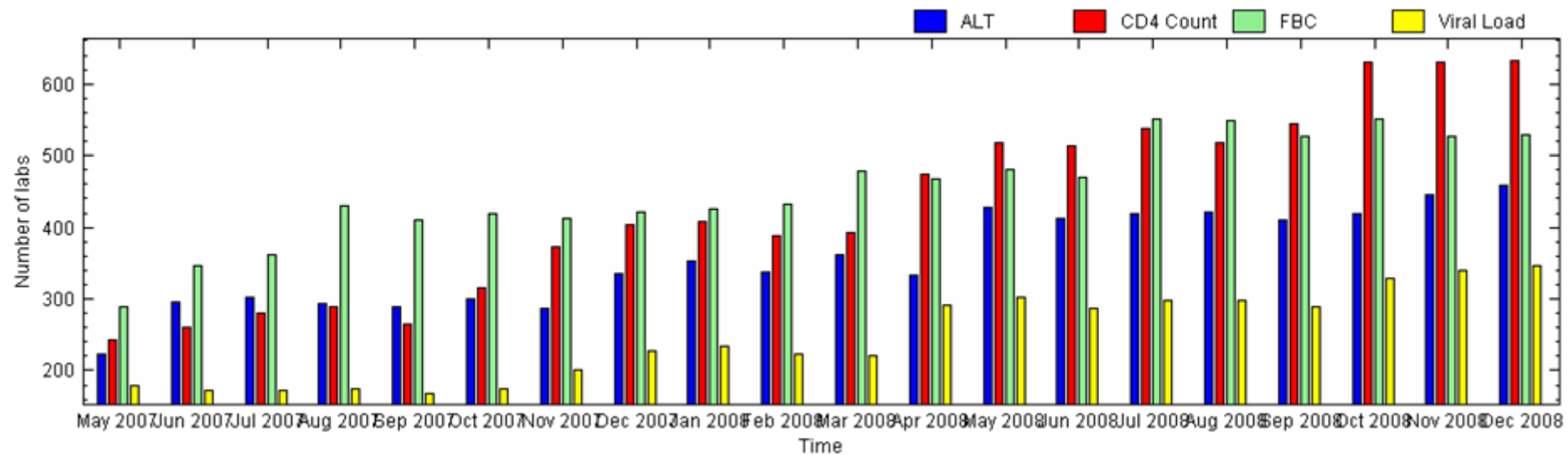
Enter laboratory testing schedule for patients who are *in-care or in-treatment*.
Note that here, *Week 0 is the week the labs are done for the first time after a patient visits a clinic.*

Test: Enter the name of the laboratory test in the leftmost box.
Done on weeks: Weeks after the patient's initial visit during which the test should be performed. Enter this a set of number separated by commas. For example: 2,4,8 indicates that the corresponding lab test should be performed two weeks, four weeks and eight week after the patient's initial visit (which is assumed to happen on week 0).
And every __ weeks thereafter:Run the lab test again each time this number of weeks pass.

Remove a test by clicking the corresponding **Delete** button.
Add a test by clicking the **Add other labs** button and fill in the new row as before. (Up to 10.)

Add other labs

Test	<input type="text" value="ALT"/>	Done on weeks	<input type="text" value="0.4"/>	and every	<input type="text" value="48"/>	weeks thereafter	<input type="button" value="Delete"/>
Test	<input type="text" value="CD4 Count"/>	Done on weeks	<input type="text" value="0.24"/>	and every	<input type="text" value="24"/>	weeks thereafter	<input type="button" value="Delete"/>
Test	<input type="text" value="FBC"/>	Done on weeks	<input type="text" value="0.4.12"/>	and every	<input type="text" value="48"/>	weeks thereafter	<input type="button" value="Delete"/>
Test	<input type="text" value="Serum lipids"/>	Done on weeks	<input type="text" value="0"/>	and every	<input type="text" value="52"/>	weeks thereafter	<input type="button" value="Delete"/>
Test	<input type="text" value="Viral Load"/>	Done on weeks	<input type="text" value="0"/>	and every	<input type="text" value="52"/>	weeks thereafter	<input type="button" value="Delete"/>



Research article

Open Access

How far will we need to go to reach HIV-infected people in rural South Africa?

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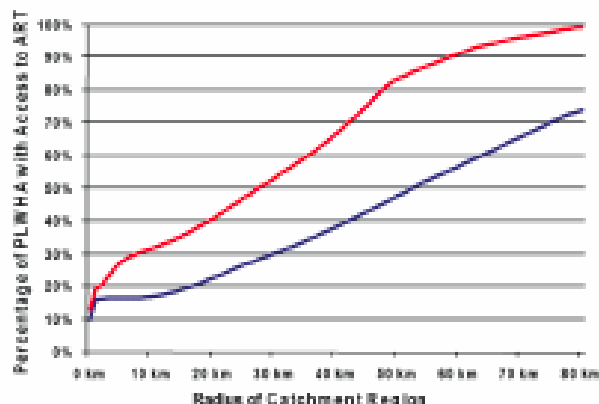
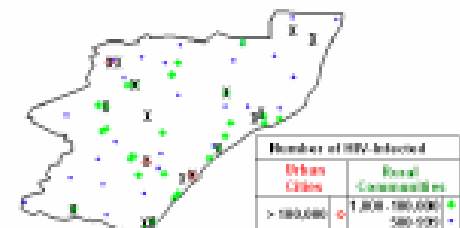


Figure 2
The estimated percentage of PLWHA living in rural areas with access to treatment as a function of the size of the catchment area radius around each HCF. We include the cases of (1) 17 HCFs (blue curve), and (2) 54 HCFs (red curve).

(a)



(b)

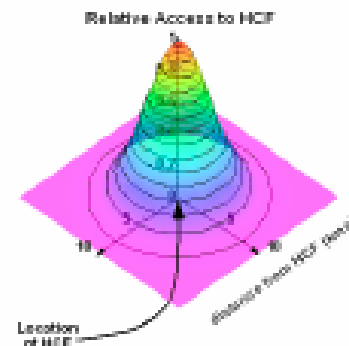


Figure 1
(a) Map of KwaZulu-Natal, indicating (with black crosses) the location of the 17 health care facilities (HCFs) that have been designated for ART rollout by the South African Government, and the spatial distribution of communities distinguished by the number of PLWHA (by both size and color).

Model 3:

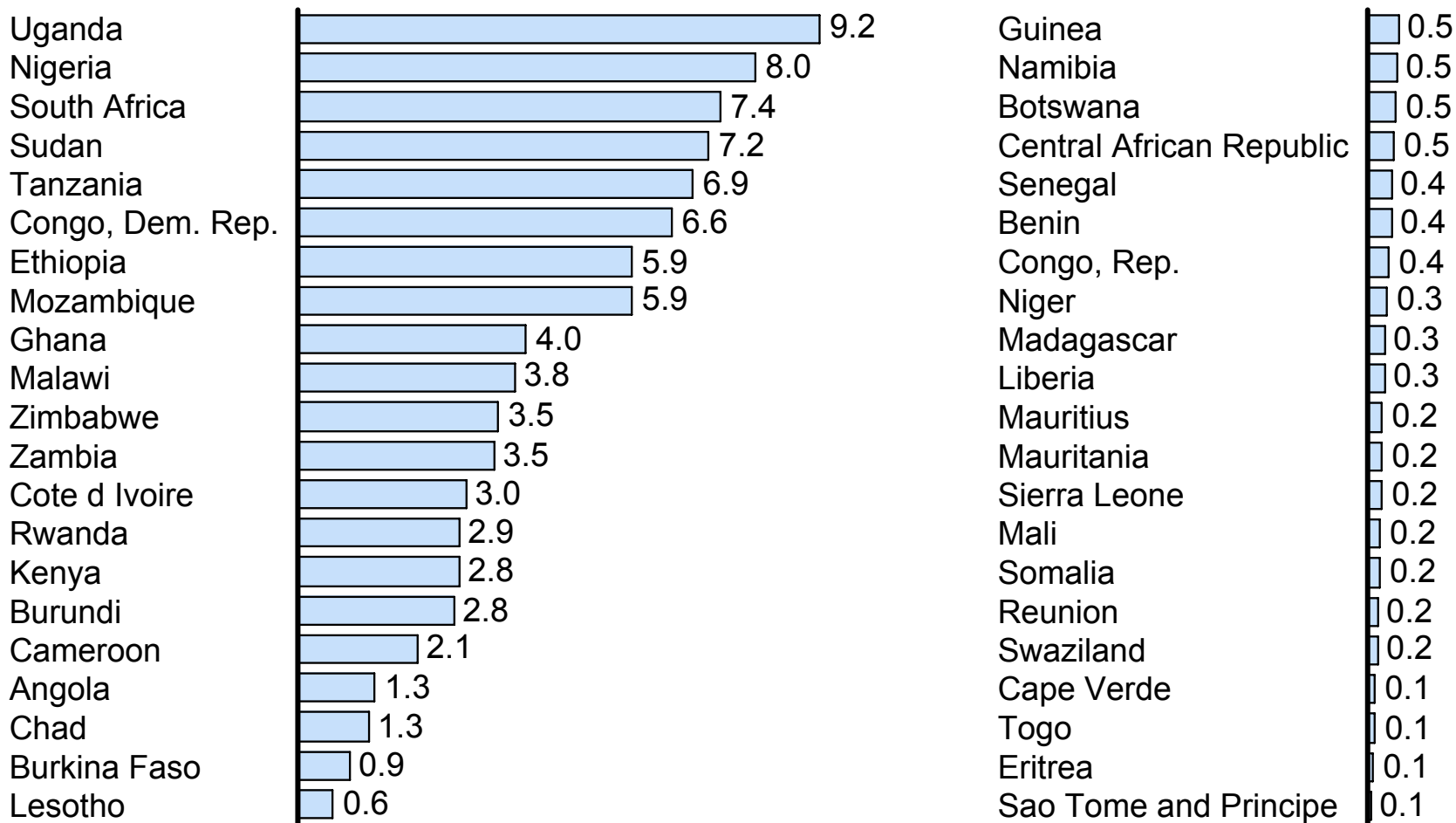
Male-circumcision clinic scale-up

- Multiple randomized controlled trials stopped early due to **substantial protective effect of adult male circumcision** on HIV infection rates in circumcised men

1 Africa contains over 95 million uncircumcised males under the age of 24, with the largest population in Uganda

Uncircumcised males in Africa* under the age of 24

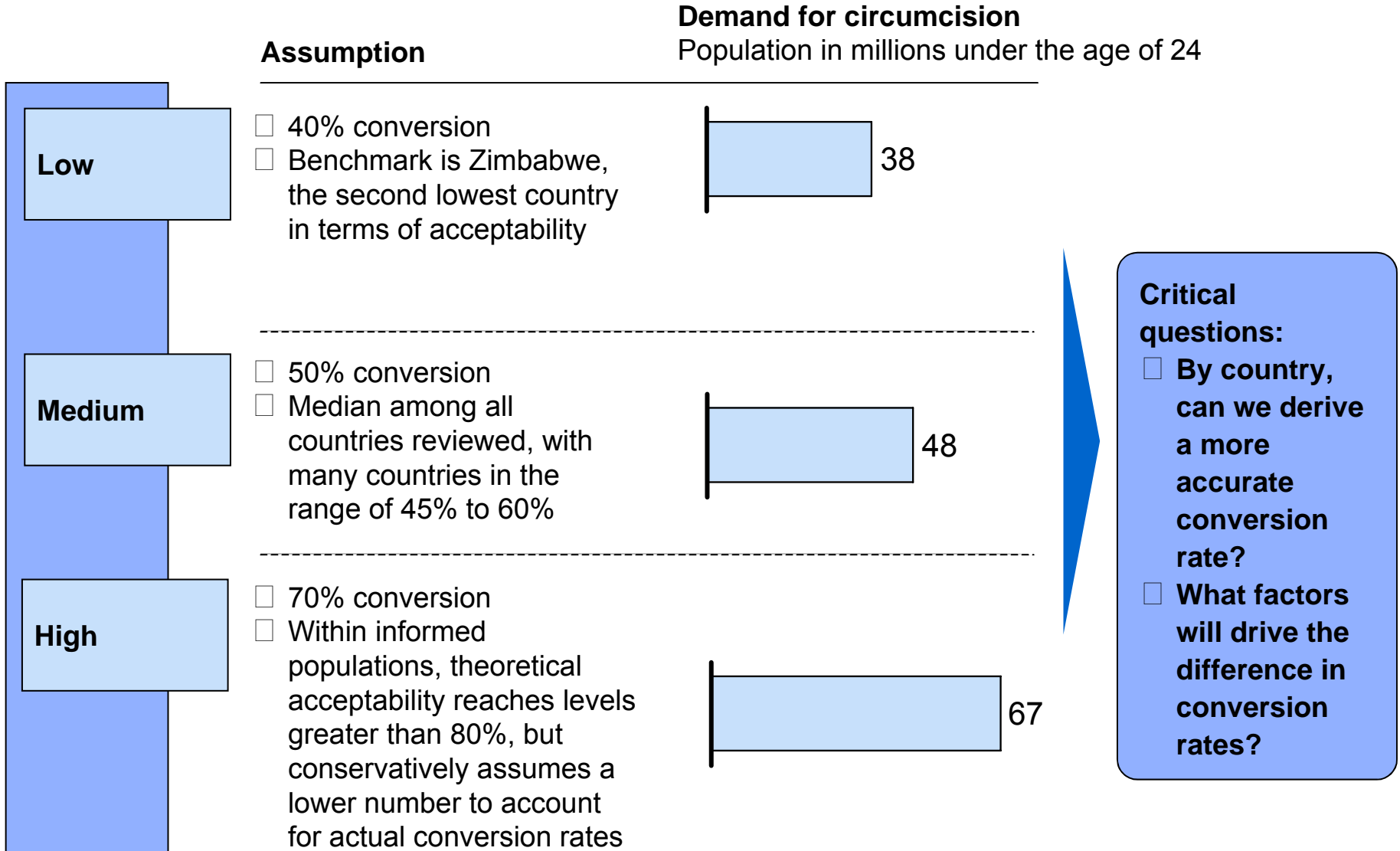
Millions



* Gambia, Guinea-Bissau, Gabon, Equatorial Guinea, Seychelles, Libya, Djibouti, Comoros, Algeria, Egypt, Morocco, Tunisia were negligible due to small population of uncircumcised young men

Source: US Census Bureau 2007; Global Insights 2007; *Male Circumcision and AIDS: The Macroeconomic Impact of a Health Crisis*, 2006; team analysis

1 Demand for circumcision in Africa could range from 40 to 70 million men under the age of 24

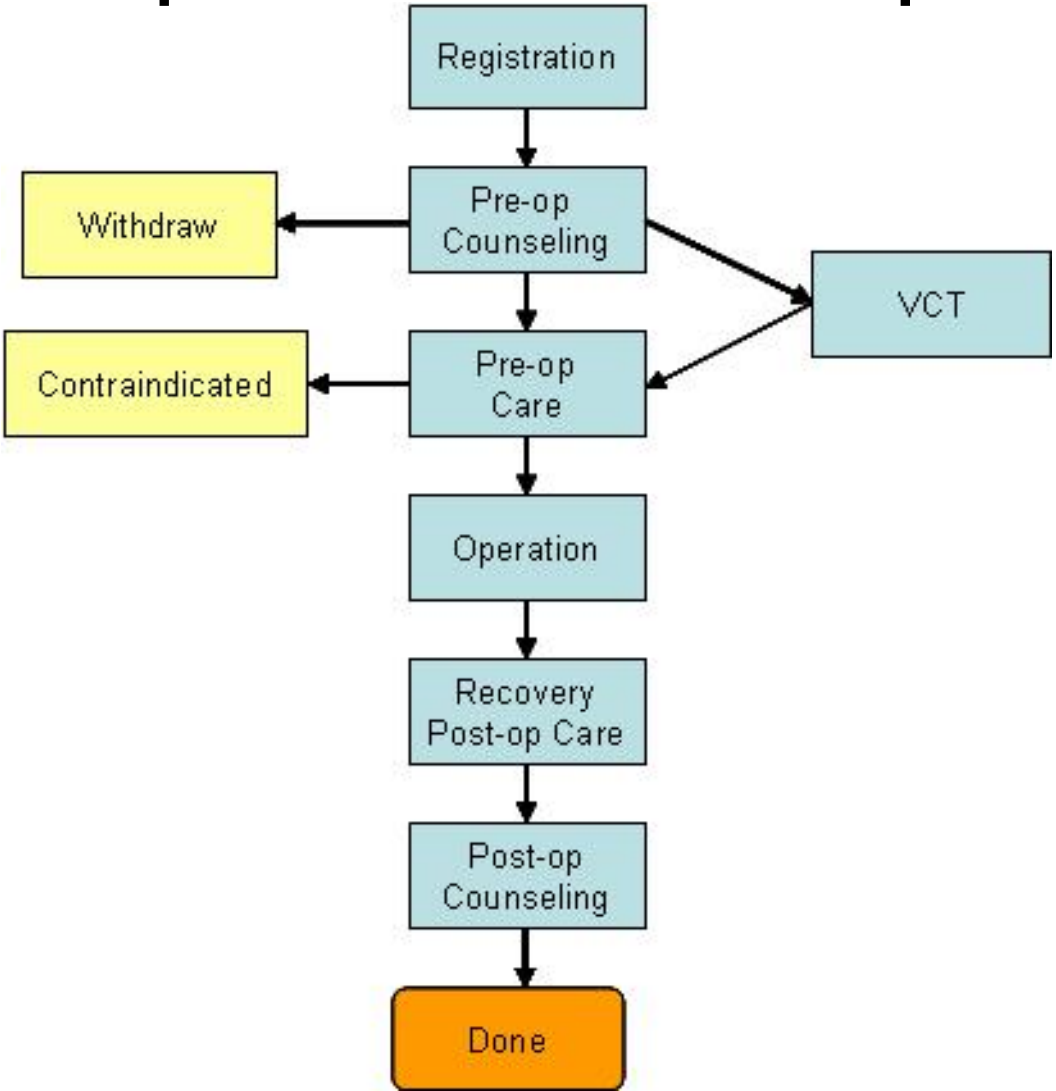


Model 3:

Male-circumcision clinic scale-up

- Multiple randomized controlled trials stopped early due to **substantial protective effect of adult male circumcision** on HIV infection rates in circumcised men
- High demand for service among general male population
- Often inadequate clinical facilities
- Complex human resource trade-offs with existing/planned HIV treatment efforts

Sample clinical flow plan:



Task-based approach

Station	Task assigned to	Mean Service time
Registration	Non healthcare worker	5 min
Pre-op Counseling	Counselor	20 min
Pro-op Care	Nurse	25 min
Operation	Doctor	45 min
Recovery and Post-op Care	Nurse	30 min
Post-op Counseling	Counselor	15 min
VCT	Phlebotomist	15 min

Queueing network

- Model clinic as an *Open Jackson Network* of M/M/s queuing processes
- Time-stationary Poisson distribution for arrivals
- Exponential distribution for processing times
- Solve for number of staff with maximum avg. queue length that user specifies

Sample model run:

	Deterministic with utilization		Stochastic with requirement that waiting time at any station is \leq (min)		
	100%	75%	60	30	10
Doctor	2	3	4	4	5
Nurse	3	4	4	5	6
Counselor	2	2	3	3	5
Non healthcare worker	1	1	2	2	2
Phlebotomist	1	1	1	1	2
Total Active Staff	9	11	14	15	20



Resource Forecast for Male Circumcision Clinic



Overall MC scale-up campaign input

Size of target population: 10000

Duration in Years: 2

Days of operation per year: 250

Hours of operation per day: 8

Waiting time less than (min): 30

Initial Visit Task Assignment

Task	Task assigned to	Average time (min)
Registration	non healthcare worker	5
Pre-op Counseling	Counselor	20
Pre-op Care	Nurse	25
Operation	Doctor	45
Recovery and Post-op Care	Nurse	30
Post-op Counseling	Counselor	15
VCT	Phlebotomist	15

Percentage go to voluntary counseling and testing (%): 70

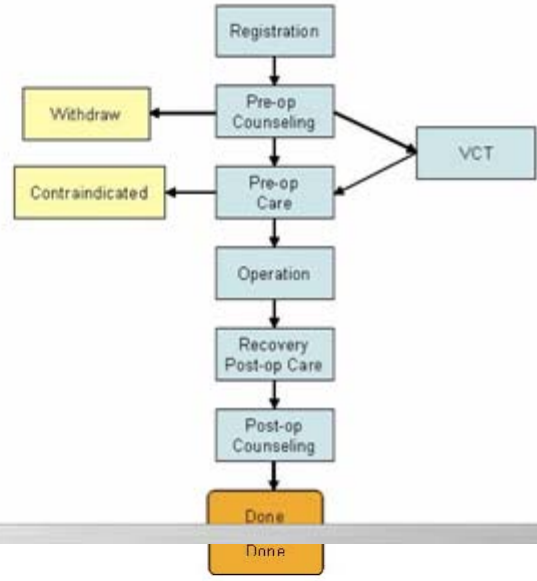
Percentage withdraw after pre-op counseling (%): 10

Percentage of contraindicated after pre-op care (%): 10

Percentage of contraindicated after pre-op care (%): 10

Percentage of follow-up patient (%): 80

Initial Visit Flow Chart

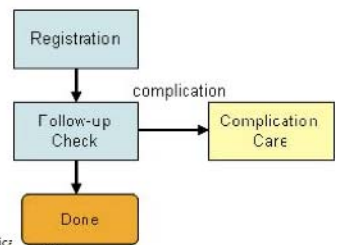


Follow-up Visit Task Assignment

Task	Task assigned to	Average time (min)
Registration	non healthcare worker	5
Follow-up Check	Nurse	20
Complication Care	Doctor	35

Percentage of complication (%): 5

Follow-up Visit Flow Chart



1 National policy will be a critical driver of a high conversion rate

Policy

Key questions

- Who will be permitted to perform M/C?
- What will be the cost to each participant?
- Where will M/C be performed?
- Will HIV testing be mandatory as pre-screening?
- How will complications be handled?
- What age group will M/C programs target?

Culture

- What is the public opinion?
- Do common religions support or hinder the MC movement?
- What has been the nature of media coverage?

Resources

- How many people can perform M/C in the country?
- Based on the operating model, what is the maximum daily capacity?
- Are there adequate educators
 - § To inform the public?
 - § To teach those who perform M/C?
 - § To ensure proper care of circumcised patients?

Existing capacity

- Who currently performs M/C?
- How is demand split between public/private (e.g. for profit, faith-based, NGOs)?
- Within the private sector what is their capacity?



"Employing OR techniques and modeling skills, the OR department has played a role in the development of long-range plans for the past 17 years. Every major system change ... (was) modeled by OR several years in advance of the actual system change. This enabled the company to grow smoothly... By modeling various alternatives for future system design, FedEx has, in effect, made its mistakes on paper. Computer modeling works; it allows us to examine many different alternatives and it forces the examination of the entire problem."

-- Frederick W. Smith, Chairman, CEO , Founder, FedEx

Summary

- OR allows you to put some order on the chaos of health delivery.
- OR and its models can be used to identify service delivery bottlenecks, and to maximize resource allocation given resource constraints.
- **It is critical for practitioners to be involved in the process of translating their knowledge into models, and for the models to be of immediate, practical use.**
- Well-designed, **practical** decision support software can provide decision makers with scientific, testable, and quantitative representations of service delivery and associated logistical systems.
- The most important step in an OR project, in particular for HIV-related issues, often turns out to be understanding and formulating the problem itself.
- Data collection and change management are big challenges in applying decision support tools in practice.

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