Risk heterogeneity in dynamical models of HIV transmission: a scoping review of parameterizations

Jesse Knight[1] and Sharmistha Mishra[1,2,3,4]

[1]Institute of Medical Sciences, University of Toronto
[2]MAP Centre for Urban Health Solutions, Unity Health Toronto
[3]Division of Infectious Disease, Department of Medicine, University of Toronto
[4]Institute of Health Policy, Management and Evaluation, Dalla Lana School of Public Health, University of Toronto

September 25, 2020

Contents

Key Messages

1. HIV transmission models have been used to answer a variety of research questions, though most have focused on projecting the population-level transmission impacts of current and future interventions.

2. Parameterizations of heterogeneity in social, biological, and intervention dimensions of simulated populations have also varied widely.

3. Among modelling studies of the transmission benefits of ART treatment as prevention (TasP):

   (a) several have assumed homogeneity in social elements of transmission risk;

   (b) even among models with transmission risk heterogeneity, most assumed homogeneity in intervention scale-up and coverage.

   In reality, heterogeneity in transmission risk can make it harder control an epidemic via TasP, and often overlaps with barriers to achieving viral suppression. Thus, such assumptions may lead to overestimated transmission impact of TasP.

4. Few modelling studies have explicitly modelled the unique vulnerabilities faced by some adolescent girls and young women (beyond older male partners), particularly in the context of transactional sex, such as higher rates of violence and lower condom use, as well as barriers to accessing prevention tools.

Table 1: [SKETCH] Modelled elements of heterogeneity in transmission dynamics and their possible relationship with intervention impacts

Dimension	Stratification	Importance
HIV	acute infection	A larger proportion of infections cannot be averted via ART.
	by CD4	Historical ART eligibility criteria & enrolment data; good indicator of HIV symptoms, morbidity, & mortality.
	by viral load	Better indicator of infectivity than CD4.
Behavioural	partnership rate	
	partnership type	
	turnover	
	key populations	identifiable groups at higher risk for acquisition & transmission;

1 Introduction

[OLD] The objectives of our review were to answer the following research questions:

1. In which contexts (geographies, populations, time periods) within SSA, and for what applications (research questions) have HIV transmission models been used?
2. What parameterizations have been used to represent risk heterogeneity in *deterministic compartmental* HIV transmission models applied to SSA?
3. How and why are particular parameterizations of risk heterogeneity and mixing in *deterministic compartmental* HIV transmission models associated with specific contexts and applications within SSA?

2 Methods

We searched MEDLINE and EMBASE via Ovid using search terms related to HIV, SSA, and transmission modelling (full search terms and hits are given in Appendix A). Duplicate studies were automatically removed. Potentially relevant studies was identified by title and abstract screening. The final selection of studies were identified by review of the full text and any available supplementary material. Data extraction also considered the full text and supplementary material. One reviewer (JK) conducted the search and data extraction.

2.1 Inclusion/Exclusion Criteria

Studies published after 2019 were included if they applied a dynamical model of sexual HIV transmission to any context within SSA. A HIV transmission model projects the number of new HIV in-

fections in a population based on initial conditions. In a *dynamical* transmission model, the number of infections projected at time t is influenced by the number of infections previously projected by the model before time t. Thus dynamical models can capture higher-order (nonlinear) population-level transmission dynamics, such as indirect benefits of prevention interventions. Models were only included if they considered sexual transmission of HIV, possibly alongside other routes of transmission, such as mother-to-child and parenteral, and possibly alongside transmission of other infectious diseases such as other STI, tuberculosis, or malaria. We excluded studies without primary modelling results, such as reviews and commentaries, as well as conference publications.

2.2 Data Extraction

Epidemic Context Studies were categorized by the geographic scale of the simulated epidemic (city, sub-national, national, super-national) and by whether multiple geographic contexts were considered. Whenever the impact of interventions was assessed, the epidemic scale was classified according to overall HIV prevalence: low ($< 1\%$), medium ($1 - 5\%$), or high ($> 5\%$).

Interventions We examined which of the following interventions were included in the model. We classified each simulated intervention as either part of *historical* interventions (typically constituting a "status-quo" scenario, and possibly including historical behaviour change), or part of *counterfactual* interventions (typically to assess intervention impact in roll-out/scale-up scenarios).

- ART CD_4: any increase in ART coverage according to a CD_4 threshold
- ART UTT: any increase in ART coverage without initiation condition ("universal test & treat")
- VMMC: voluntary medical male circumcision
- PrEP: pre-exposure prophylaxis, by any route of administration
- Condoms: any intervention which was simulated to increase condom use
- Partners: any intervention which reduces the rate of partnership formation
- STI: any intervention reducing HIV transmission by reducing STI symptom burden
- Generic: an unspecified generic HIV prevention interventions

For each simulated intervention scenario, we noted which combinations of interventions were considered, including combinations of historical interventions, counterfactual interventions on top of historical interventions, and combinations of counterfactual interventions. We categorized each counterfactual simulated intervention as focusing one of the following risk groups: all women; all men; all people; young women; young men; all young people; FSW; clients; MSM; other generic high or low risk group. For studies that simulated historical or counterfactual interventions reaching multiple risk groups concurrently, such as "80% ART coverage overall", we noted whether intervention coverage was assumed to be equal across modelled risk groups, possibly ignoring historical gaps/future challenges in reaching higher risk groups.

We noted whether each study quantified the impact of counterfactual interventions on each of the following outcomes: HIV epidemic (incidence, prevalence, total infections, and/or mortality); reproduction number; transmitted drug resistance; and any economic analysis.

Risk Heterogeneity Risk heterogeneity was identified in compartmental models as population stratifications other than age, health state, or intervention involvement that conferred differential risk of HIV acquisition and/or transmission. We documented the defining characteristics of modelled risk groups, including: sex, different rates of partnership formation, and different types of partnerships formed. We noted whether each of the following key populations was included in the model: female sex workers (FSW); male clients of FSW (SWC); adolescent girls and young women (AGYW); men who have sex with men (MSM); and people who inject drugs (PWID).

We noted which of the following characteristics were used to define simulated sexual partnerships: the risk groups involved; different volumes of sex (total number coital acts per partnership); and different levels of condom use. We noted whether simulated partnerships represented any of the following identifiable types: main/spousal; casual/extramarital; commercial/sex work; transactional (exchange of gifts/favours for sex, outside the context of formal sex work). Finally, we noted whether models simulated any degree of assortative vs proportionate partnership formation (mixing) between risk groups. If some partnership types were only formed by certain risk groups, mixing was automatically considered assortative.

We additionally noted the number of unique age groups, the nature of age group mixing—proportionate, assortative without age differences, or assortative with age differences (e.g. younger females with older males)—and whether age conferred any additional risk differences beyond mixing (e.g. higher rates of partnership formation). Finally, we counted the number HIV infection states modelled (excluding treatment), and noted which characteristic was used to define the states, including: early infection (must include increased infectivity), WHO clinical criteria, $CD4$ count, and viral load.

3 Results

Database search identified 1367 publications, of which 100 studies met the inclusion criteria (Figure 1). Several models of HIV progression and treatment were excluded as they did not model HIV transmission, and several models simulating vertical transmission were excluded as they were not dynamical. Table 2 summarizes the basic characteristics of the models in each study.

3.1 Context & Applications

Most studies simulated HIV transmission at the national level, including 43 single-country and 11 multi-country analyses. Studies also explored super-national (4), sub-national (14), and city-level (11) epidemic scales. South Africa was the most common context simulated (48 studies, Figure 2), but was not disproportionately represented among SSA countries, since the number of transmission modelling studies per million PLHIV as of 2019 in South Africa (6.67) was not above the SSA median (10). Kenya was the next most common with 25 modelling studies.

Table 2: Basic characteristics of transmission models used

Model Characteristic		Studies (%)
Deterministic		97 (97)
Compartmental		100 (100)
Population stratification	Sex	66 (66)
	Age	37 (37)
	Risk[1]	76 (76)
Key populations included	FSW	33 (33)
	SWC	29 (29)
	MSM	10 (10)
	PWID	0 (0)
	AGYW	TBD
Historical interventions	Generic	17 (17)
	ART	62 (62)
	VMMC	26 (26)
	Condoms	32 (32)
	Partners	10 (10)
	STI	5 (5)
Counterfactual interventions[2]	ART CD_4	32 (39)
	ART UTT	31 (37)
	VMMC	26 (31)
	Condoms	17 (20)
	PrEP	30 (36)
	STI	5 (6)
Intervention outcomes[2]	HIV impact	
	"R"	
	Drug resist.	
	Economic	

[1] Risk = any stratification other than sex that confers differential HIV risk, or any differential risk by age group; this definition is different than that used to *count* risk groups. [2] Reported % among studies examining any counterfactual intervention. See 2.2 for additional definitions.

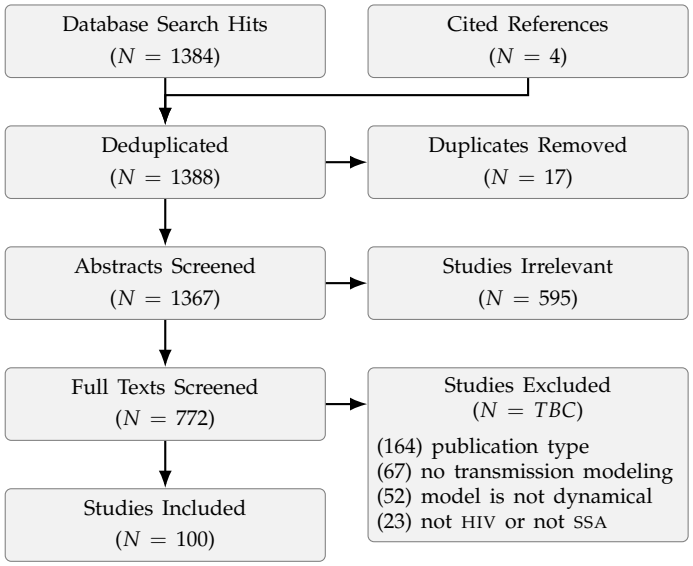


Figure 1: PRISMA flowchart of study identification [numbers not final]

3.2 Interventions

The population-level prevention benefits of increased ART coverage was simulated in 45 studies, including 32 studies examining increased coverage under CD_4 thresholds, and 31 studies examining UTT (18 studies examined both). Increasing ART coverage under any eligibility criteria was rarely prioritized to any risk group (only 10 of 45 studies), although several studies by Anderson et al. [2] explored prioritization of ART to women, men, FSW, and MSM under UTT (Figure 3). Before 2015 (WHO began recommending UTT), 31 and 24 studies examined non-prioritized scale-up of ART under CD_4 thresholds and UTT respectively, while only 2 and 9 examined prioritized scale-up.

Most studies examining VMMC interventions did not explore prioritization to risk groups among men. By contrast, counterfactual PrEP interventions were prioritized to a wide range of risk groups, especially FSW. Among simulated behavioural interventions, condom promotion was often prioritized to sex work, whereas decreasing partnership formation rates was simulated among women, men, FSW, and MSM mostly by Anderson et al. [2]. The most commonly simulated historical interventions were increasing ART coverage (62), condom use (32), and VMMC (26), followed by a generic reduction in force of infection (17), according either to HIV prevalence as in [3], or calendar time as in [**Awad2015a**]. The inclusion of any historical intervention increased with publication year ($p = 0.001$).

Regarding intervention combinations, Figure 4 illustrates the number of studies simulating: (a) combinations of multiple historical interventions; (b) combinations of counterfactual interventions and historical interventions; and (c) combinations of counterfactual interventions. Additional ART scale-up, VMMC, and PrEP interventions were often simulated against historical increases in VMMC, condom use, and especially ART scale-up. By contrast, behavioural interventions (increasing condom use & decreasing partners) were less likely to be simulated against historical interven-

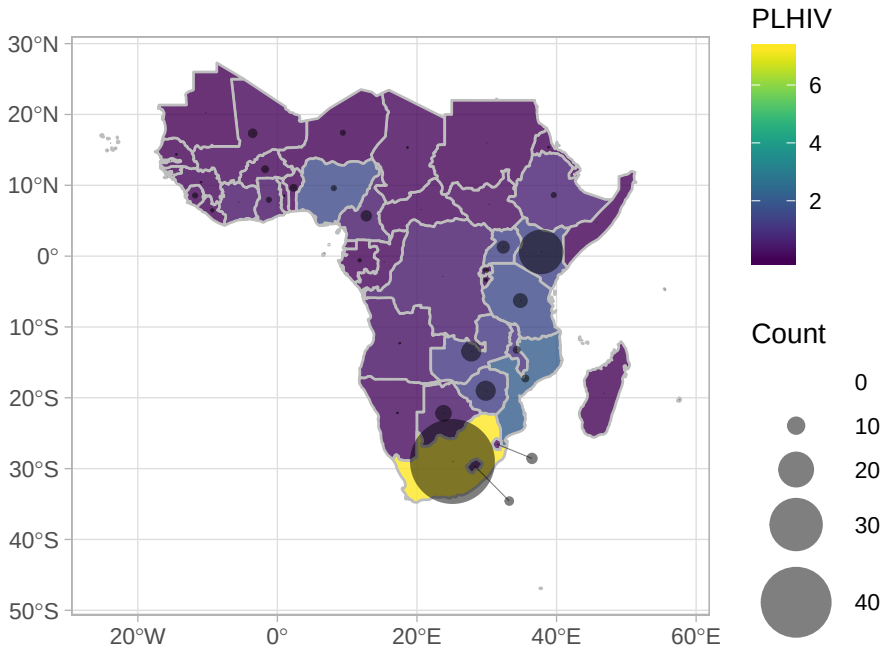


Figure 2: Number of dynamical HIV transmission modelling studies per country (circle area) vs million PLHIV (fill) as of 2019 from [1].

tions. Counterfactual combination interventions most often included ART (especially UTT), VMMC, and PrEP. Table 3 summarizes the complete selection of particular combinations explored.

3.3 Parameterizations of Risk Heterogeneity

Risk Groups Among compartmental models, the median (IQR) number of risk groups modelled was 4.5 (2, 8) when considering sex as a risk stratification, and 2.5 (1, 4) otherwise. In univariate analysis, the number of risk groups increased significantly with publication year ($p = 0.029$), and in studies assessing counterfactual VMMC and PrEP interventions ($p = 0.014$ and $p = 0.013$, respectively). Besides sex, risk groups were primarily defined by rates of partnership formation (63), followed by different types of partnerships formed (34). Baseline turnover of individuals between at any risk groups was simulated in 23 studies, while an additional 8 studies simulated turnover only to maintain constant risk group proportions under differential HIV-related mortality.

Among 37 studies that stratified the population by age, [TODO: mixing, explicit age risk].

Key Populations & Partnership Types FSW were modelled in 33 studies, although 21 additional studies simulated risk groups having similar relative rates of partnership formation [TODO: up-

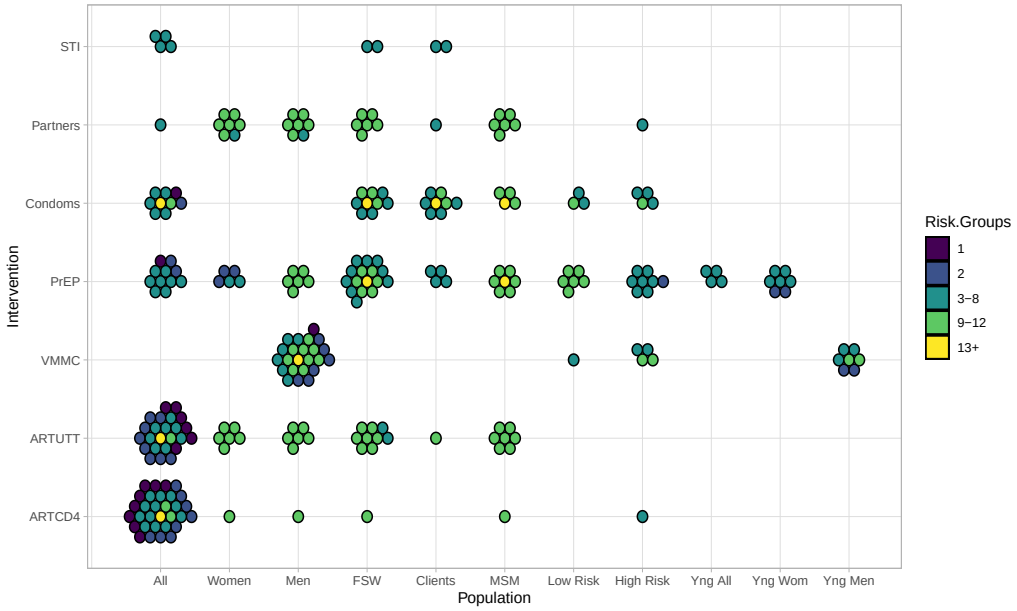
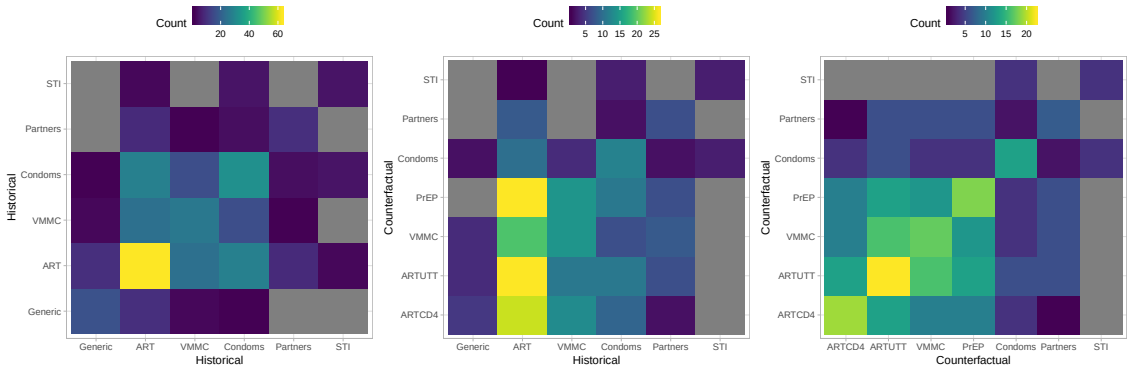


Figure 3: Number of studies simulating counterfactual interventions prioritizing specific risk groups (points), and the total number of risk groups in each model (fill colour).

Studies may appear more than once if multiple prioritized populations and/or interventions were simulated.



(a) Historical combinations (b) Counterfactual with historical (c) Counterfactual combinations

Figure 4: Co-occurrence of modelled historical and counterfactual interventions

Historical: simulated to reflect existing interventions; Counterfactual: hypothetical interventions whose impact is being evaluated; See 2.2 for additional definitions.

Table 3: Counterfactual combination interventions simulated

Intervention					Studies
ART	VMMC	PrEP	Condoms	Other	
CD4/UTT	VMMC				3
CD4/UTT	VMMC	PrEP			3
CD4/UTT	VMMC	PrEP	Condoms		1
CD4/UTT	VMMC	PrEP	Condoms	Partners	1
CD4/UTT		PrEP			1
CD4/UTT				Generic	2
CD4		PrEP			3
CD4			Condoms		1
UTT	VMMC	PrEP		Partners	5
UTT	VMMC		Condoms		1
UTT		PrEP	Condoms		1
UTT			Condoms		1
	VMMC	PrEP		Cash	1
		PrEP	Condoms		1
			Condoms	Partners	1
			Condoms	STI	4

See 2.2 for intervention definitions.

date based on clearer definitions]. Sex work partnerships were explicitly modelled in 23 studies, defined by: lower volumes of sex (XX), higher condom use (XX), or both (XX). Casual partnerships were also modelled in 23 studies, of which XX also modelled sex work; casual partnerships were similarly defined by: lower volumes of sex (XX), higher condom use (XX), or both (XX).

The median (IQR) number of HIV infection states modelled was 3 (2, 4.5), and 63% of studies considered transient increased infectivity associated with acute infection.

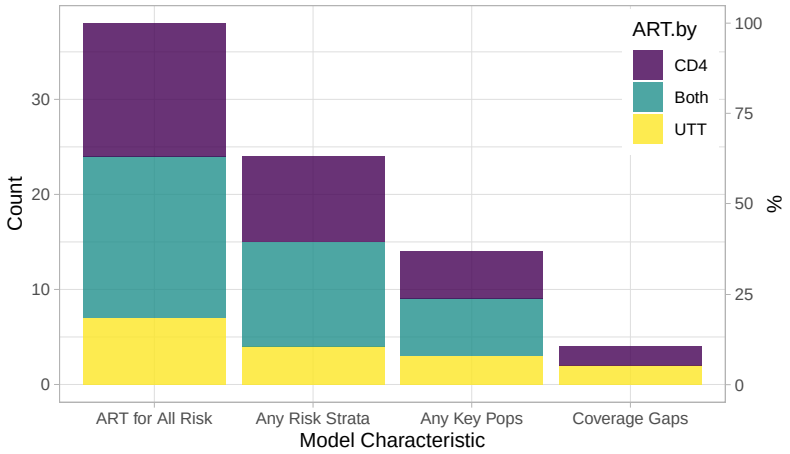


Figure 5: Model heterogeneity cascade among studies assessing counterfactual scale-up of ART equally across all modelled risk groups. Coverage gaps represents acknowledgement of differential (lower) coverage among key populations.

4 Discussion

- we found (brief): large variability in application of transmission models, and parameterization of risk heterogeneity w.r.t. biological, social, and intervention dimensions
- brief context of heterogeneity importance:
  - core group theory: explosive growth, lower endemic equilibrium
  - more difficult to "control" (higher R_0)
- TasP studies:
  - inspired by individual-level prevention benefits (U=U) & push for 90-90-90: large interest in scaling up ART coverage
  - many studies explored possible transmission benefits
  - however: 4 important assumptions often made:
    - no acute infection – could represent a substantial proportion of infections "unpreventable" via TasP
    - homogeneity in risk – core group theory & model comparison studies suggest risk heterogeneity makes epidemic harder to control
    - no turnover – could thus overestimate the ease of reaching high ART coverage in risk groups with high turnover given delays in linkage and viral suppression
    - homogeneity in intervention coverage – could overestimate impact as challenges to increasing cascade in key populations are overlooked
  - overall: could result in overestimation of the transmission impact of TasP
  - some ideas above may be generalizable to other interventions
- AGYW & Transactional sex:
  - was rarely explicitly modelled (defined: lower condom use, higher transmission probability, violence, barriers to accessing prevention tools)
  - FSW were modelled often, including prioritized interventions to FSW
  - but: emerging evidence of access gap that parallels periods of potentially highest transmission risk
  - represents important gap in modelling literature
- challenges to parameterizing heterogeneity
  - biological
    - debate over the importance, duration/size, & variability of acute phase
  - behavioural:
    - lack of data: number of studies (due to cost), internal (reliability), and external (representativeness) of studies.
    - difficulty of stratifying calibration targets (prevalence, incidence) by risk groups for the same reasons
    - amplified challenges for key populations
    - similar challenges for stratified intervention engagement data
    - costing & engagement highly context/implementation-specific (HTPN)

A Search Terms

Our search strategy and component results are as follows, where `[section]` refers to the result from another section, `term/` denotes a MeSH term, and `.mp` searches the main text fields, including title, abstract, and heading words.

Table 4: Summary of search terms & results

	Term	Hits
1	1,369,153	`[model]`
2	954,470	`[hiv]`
3	982,505	`[ssa]`
4	2190	`1 AND 2 AND 3`
5	1384	`4 NOT [exclude]`

Table 5: Exclusion

	Term	Hits
1	2190	`[model] AND [hiv] AND [ssa]`
2	2160	`1 NOT animal/`
3	2155	`limit 2 to english language`
4	2125	`limit 3 to yr="1860 - 2019"`
5	1384	`remove duplicates from 4`

Table 6: Search Terms related to modelling

	Hits	Term
1	238,076	`model, theoretical/`
2	334,921	`model, biological/`
3	302,802	`computer simulation/`
4	196,814	`patient-specific modeling/`
5	67,459	`monte carlo method/`
6	32,801	`exp stochastic processes/`
7	455,312	`(model* ADJ3 (math* OR transmission OR dynamic* OR epidemi* OR compartmental OR deterministic OR individual OR agent OR network OR infectious disease* OR markov OR dynamic* OR simulat*)).mp.`
8	1,369,153	`OR/ 1-7`

Table 7: Search Terms related to HIV

	Term	Hits
1	290,863	exp HIV/
2	651,624	exp HIV infections/
3	753,274	(HIV OR HIV1* OR HIV2* OR HIV-1* OR HIV-2*).mp.
4	369,182	hiv infect*.mp.
5	538,214	(human immun*deficiency virus OR human immun* deficiency virus).mp.
6	216,228	exp Acquired Immunodeficiency Syndrome/
7	235,971	(acquired immun*deficiency syndrome OR acquired immun* deficiency syndrome).mp.
8	954,470	OR/ 1-7

Table 8: Search Terms related to SSA

	Term	Hits
1	3512	Angola/ OR Angola.mp.
2	9273	Benin/ OR Benin.mp.
3	5809	Botswana/ OR Botswana.mp.
4	9983	Burkina Faso/ OR Burkina Faso.mp.
5	2055	Burundi/ OR Burundi.mp.
6	16,822	Cameroon/ OR Cameroon.mp.
7	1196	Cape Verde/ OR Cape Verde.mp.
8	15,416	Central African Republic/ OR Central African Republic.mp. OR CAR.ti.
9	3075	Chad/ OR Chad.mp.
10	995	Comoros/ OR Comoros.mp.
11	13,737	Democratic Republic of the Congo/ OR Democratic Republic of the Congo.mp. OR DRC.mp.
12	959	Djibouti/ OR Djibouti.mp.
13	1131	Equatorial Guinea/ OR Equatorial Guinea.mp.
14	1437	Eritrea/ OR Eritrea.mp.
15	35,959	Ethiopia/ OR Ethiopia.mp.
16	4500	Gabon/ OR Gabon.mp.
17	6626	Gambia/ OR Gambia.mp.
18	25,213	Ghana/ OR Ghana.mp.
19	360,920	Guinea/ OR Guinea.mp.
20	2625	Guinea-Bissau/ OR Guinea-Bissau.mp.
21	9730	Cote d'Ivoire/ OR Cote d'Ivoire.mp. OR Ivory Coast.mp.
22	46,917	Kenya/ OR Kenya.mp.
23	1649	Lesotho/ OR Lesotho.mp.
24	4239	Liberia/ OR Liberia.mp.
25	11,386	Madagascar/ OR Madagascar.mp.
26	16,367	Malawi/ OR Malawi.mp.
27	9111	Mali/ OR Mali.mp.
28	1573	Mauritania/ OR Mauritania.mp.
29	2373	Mauritius/ OR Mauritius.mp.
30	8502	Mozambique/ OR Mozambique.mp.
31	3818	Namibia/ OR Namibia.mp.
32	35,455	Niger/ OR Niger.mp.
33	82,192	Nigeria/ OR Nigeria.mp.
34	13,547	Republic of the Congo/ OR Republic of the Congo.mp. OR Congo-Brazzaville.mp.
35	1545	Reunion/
36	7597	Rwanda/ OR Rwanda.mp.
37	342	"Sao Tome AND Principe"/ OR "Sao Tome AND Principe".mp.
38	16,674	Senegal/ OR Senegal.mp.
39	1566	Seychelles/ OR Seychelles.mp.
40	5456	Sierra Leone/ OR Sierra Leone.mp.
41	4667	Somalia/ OR Somalia.mp.
42	114,536	South Africa/ OR South Africa.mp.
43	1193	South Sudan/ OR South Sudan.mp.
44	21,680	Sudan/ OR Sudan.mp.
45	2409	Swaziland/ OR Swaziland.mp. OR Eswatini/ OR Eswatini.mp.
46	32,442	Tanzania/ OR Tanzania.mp.
47	3749	Togo/ OR Togo.mp.
48	37,399	Uganda/ OR Uganda.mp.
49	13,506	Zambia/ OR Zambia.mp.
50	15,755	Zimbabwe/ OR Zimbabwe.mp.
51	482,060	exp africa south of the sahara/ OR sub-saharan.mp. OR south of the sahara.mp.
52	982,505	OR/ 1-51