The Origins of Epidemic HIVs Date to a Unique Window of Opportunity for the Initial Spread of SIV Infections Transmitted to Human Populations

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Abstract

Background: The processes that permitted a few SIV strains to emerge epidemically as HIV-1 and HIV-2 groups are unknown. Paradigmatic theories leave several loose ends unexplained, in particular regarding timing and geographical origin of HIV groups.

Methods: We performed new molecular clock analyses to time SIV/HIV divergence. We reviewed HIV-1 parenteral and sexual transmissibilities, and the co-factors genital ulcer disease (GUD) and lack of male circumcision. For all relevant geographic areas, we surveyed medical colonial literature, for incidences of GUD and injection campaigns, and primary ethnographic literature, for circumcision data, at the ethnic group level. We built epidemiological simulations of SIV spread in promiscuous cities with various sizes, GUD incidences, and circumcision rates.

Results: Molecular clock analysis on the newly reported SIVs narrows the time intervals (roughly 1880-1940) for all transfers to humans, in contrast to HTLV. Apart from unsafe injections, other factors seem to be necessary to permit SIV adaptation through serial transmission in this time frame only. While HIV-1 parenteral transmissibility (roughly 1% per-reuse) is higher than its common per-act sexual transmissibility, GUD involvement raises the latter to 4-32%. We found that, coinciding in time with MRCAs of all HIV epidemic groups, intense GUD outbreaks (e.g., with ulcerative syphilis incidences 100-300 times higher than in mid-20th century) occurred at the colonial cities. Moreover, among 12 relevant colonies, only in 3 (Cameroon, Belgian Congo, and Cote d'Ivoire) circumcision rate in major cities was low (50-80% versus near 100% in the others) and HIV groups did emerge only in them. Our simulations suggest that the odds of SIV initial spread were much higher in these cities at their intense GUD period (1920-1945), than with other conditions (rarified GUD, universal circumcision, or small towns).

Conclusions: The timing of HIV emergence fits better GUD-intensive periods in nascent cities, than the periods of higher injection, and urbanization intensities. Early HIV epicenters arose only in cities that had relatively low circumcision rates. These results suggest that intense GUD, and non-circumcision, in promiscuous urban centers together contributed to HIV emergence and adaptation. Our results imply a zoonotic danger posed by GUD, and recommend its monitoring, particularly in areas where male circumcision is less common.

Background

HIV-1 group M descends from SIVcpz endemic in chimpanzees[1], and group O has closest SIV relatives in gorillas (SIVgor) from West Central Africa[2]. HIV-2 descends from SIVsmm, endemic in West African sooty mangabeys[3]. While bushmeat handling transmits SIVs to humans, the process that permitted epidemic emergence remains a matter of debate[4,5]. The countries where these viruses formed their early human epicenters were the Democratic Republic of Congo (DRC), Cameroon, and Côte d'Ivoire, respectively.

Objectives: To understand the timing and the causes of HIV emergence.

I. Timing the splits between HIVs and SIVs

Methods

- Bayesian relaxed clock analysis implemented in BEAST[6].
- For SIVcpz-HIV-1-M: partial *pol* gene sequences (nucleotide 3887 to 4775 according to the HXB2 numbering) from both recently obtained SIVcpz[2], and additional SIVcpz (X52154, AY169968 and AF382828), and HIV-1-M sequences previously analyzed by Lemey et al. (2005)[7].
- For SIVgor–HIV-1-O: partial *pol* gene sequences (nucleotide 4230 to 4775 according to the HXB2 numbering) from three SIVgor[1], two SIVcpz (U42720 and X52154), and HIV-1-O sequences previously analyzed by Lemey et al. (2004)[8].
- Markov Chain Monte Carlo (MCMC) analyses combined with a Bayesian skyline plot model[6].
- Normal prior distribution on the TMRCA for both HIV-1-M and HIV-1-O, based on published datings[8-10]. Posterior distributions obtained by MCMC runs investigated using a Tracer.

Results

HIV group	TMRCA with closest SIV	Intragroup TMRCA
HIV-1-M	1876 (1847-1907)	1921 (1908-1933)[9-11]
HIV-1-O	1741 (1606-1870)	1920 (1890-1940)[8]
HIV-2-A	1889 (1856-1922)	1940 (1924-1956)[12]
HIV-2-B	1889 (1856-1922)	1945 (1931-59)[12]

Table 1. Estimates, with 95% CI, of TMRCA with closest SIVs (made in this study), and of intragroup TMRCA (from previous studies). Each transfer to humans happened between the two dates, most probably nearer the later.

Different temporal patterns for HIV and HTLV

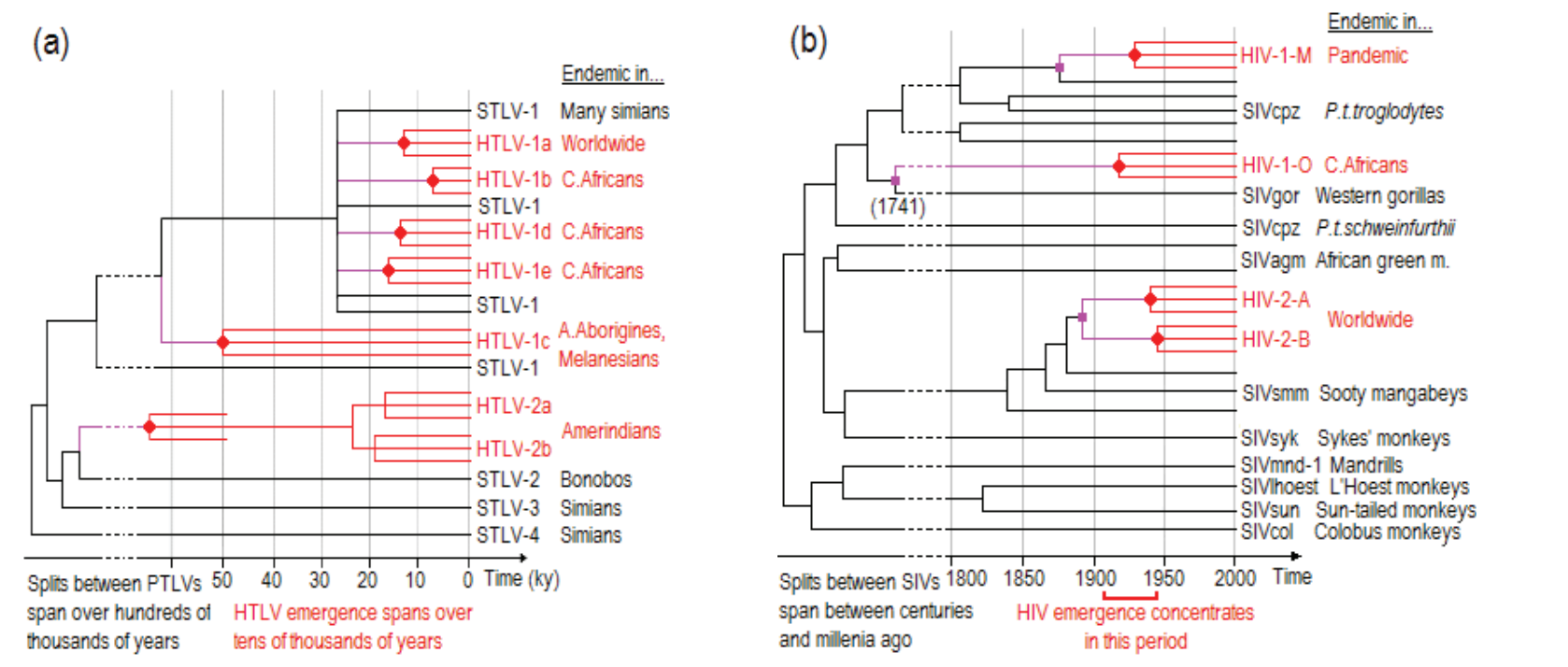

Figure 1. Human T-cell lymphotropic viruses (HTLV) (a) emerged in humans many millenia ago, and at different times[13,14], in contrast with HIV (b).

Conclusions: Transfer of HIV to humans happened in a limited timeframe compared with HTLV. Epidemic emergence was only in 1910-45.

II. Unresolved issues concerning HIV origins

First (classical) Timing Paradox: why only in 20th century? Proposed driving factors:

- Unsterile injections serially transmitted SIV between acutely infected people, improving its adaptation[4].
- Hunting intensification, forced labour, social changes, urbanization, and increased human mobility[5].

Examining the timings of the proposed risk factors

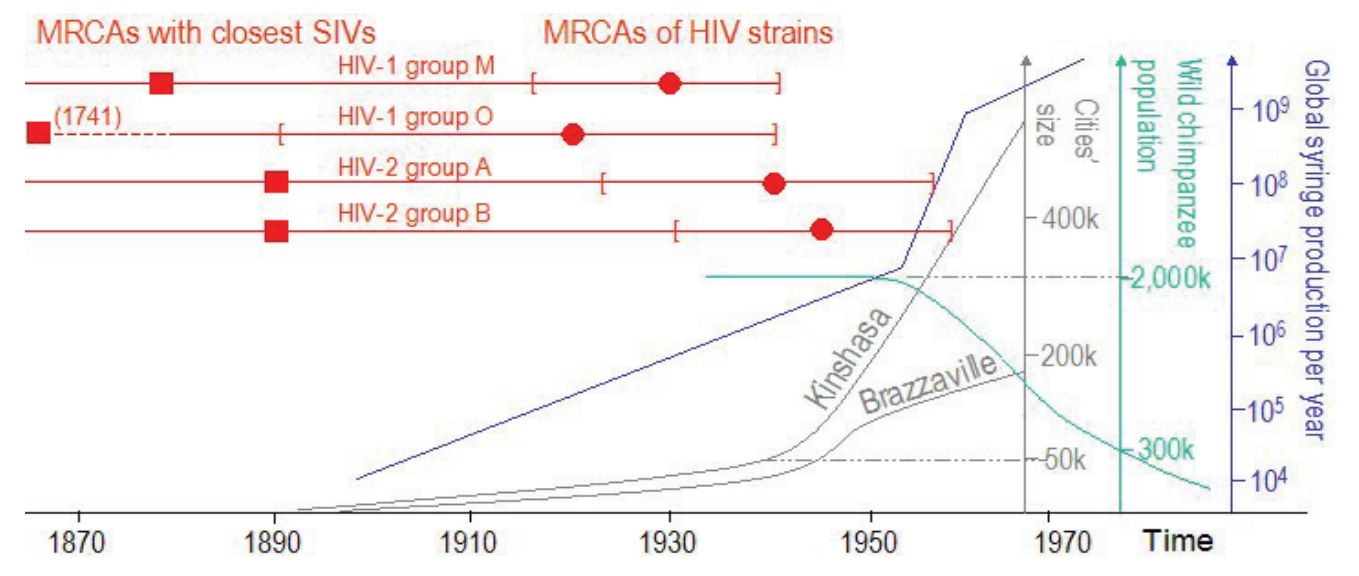

Figure 2. Injections and cities boomed after 1950; chimpanzee numbers collapsed after 1960, reflecting intensified hunting.

There is a **Second Timing Paradox:**

Why no new successful HIVs emerging around 1950-70, when all proposed factors, urbanization, injections, and hunting, intensified (figure 2), and why four HIVs took-off well before that period?

Other unsolved problems:

- Why so few successful HIV groups (since bushmeat handlers commonly acquire SIV)?
- Exactly two successful HIV-1 groups (M and O) emerged in the vast areas of chimpanzees and gorillas[1,2]. Are they two just by chance, or can we make sense of this?

III. Investigating potential driving factors

Methods

- We reviewed sexual and parenteral HIV-1 transmissibilities, and the effects of STDs, genital ulcer diseases (GUD), viral load, circumcision, and acute infection.
- For the relevant countries, and for the period 1885-1960, we researched the epidemics of STDs, injection campaigns, patterns of sexual behaviour, and the demographic history of cities.
- As sources, we used Belgian, French, Portuguese, and British articles and databases on tropical medicine, colonial history, and demography, and documents in Afrika-archief, Ministerie van Buitenlandse Zaken, Brussels, Belgium, in Centre d' Archives Outre-Mer, Aix-en-Provence, and in Institut de Médecine Tropicale du Service de Santé des Armées, Marseille, France.

Results

HIV-1 Transmissibilities

- HIV-1 per-reuse transmissibility of unsafe intravenous injections (around 1%[15]) is higher than standard per-act sexual transmissibility[16].
- However, involvement of GUD dramatically increases the later to a 4-32%[16,17] (figure 3).
- The ulcer is portal of entry and raises CCR5 expression.
- Lack of circumcision increases men's risk by a factor of 2-2.5 in long observational studies, and by a factor of 6-10 on a per-act basis[17,18].

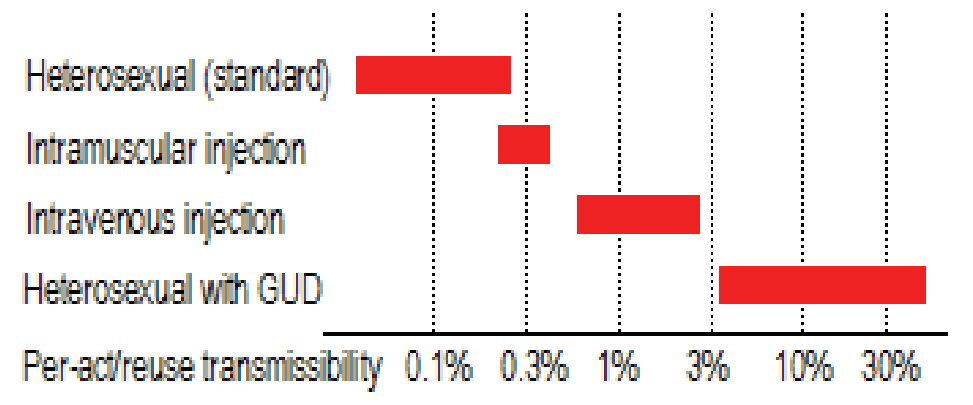

Figure 3. HIV-1 transmissibilities

GUD epidemics in equatorial Africa

- GUDs were virtually absent from the forested areas where chimpanzees and s.mangabeys live up to 1885[19].
- Then, syphilis, chancroid, and lymphogranuloma venereum (LGV) invaded, as colonial systems developed, around towns and enterprises.
- Rapid city growth led to male-biased sex ratios, thus promoting commercial sex work (CSW) and high GUD incidences.
- Better health systems after 1930, and penicillin introduction in 1945-47, reduced these diseases' incidences.
- Genital herpes only became important as cause of genital ulcers in Africa after 1980[20] (fig. 5).

The example of Leopoldville (now called Kinshasa)

By researching colonial health reports (Afrika-archief, Brussels)[21], we gathered, for Leopoldville: demographic data; recorded cases of syphilis, chancroid, LGV; the varying proportion of syphilis cases which were primo-secondary (PSS) (the only genital ulcer-causing stages).

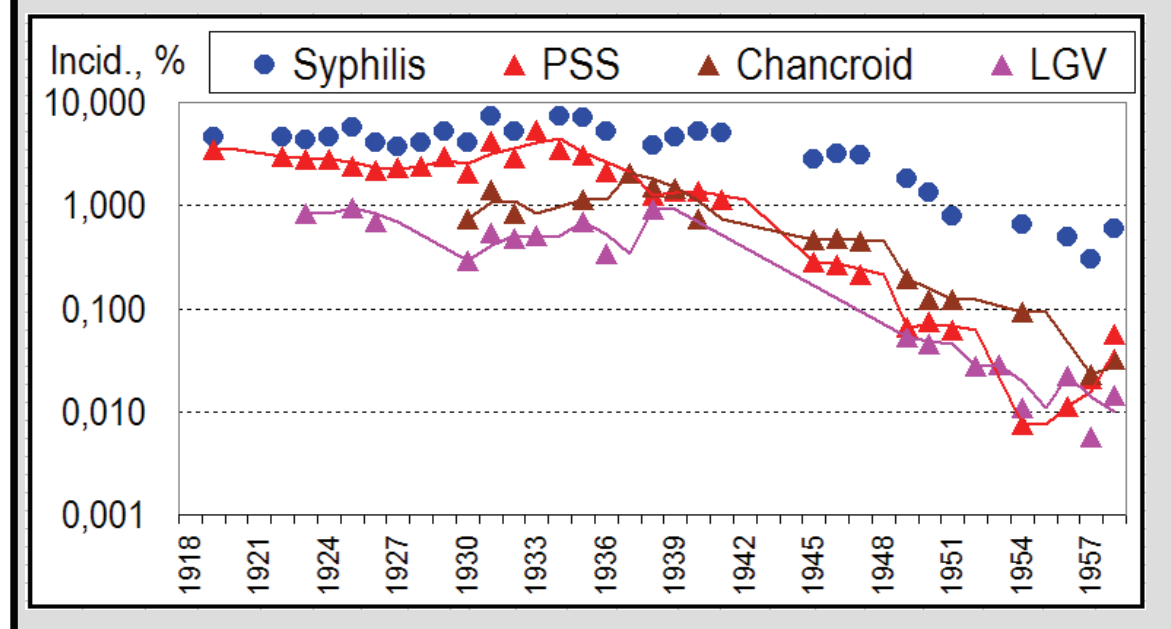

Figure 4. Annual incidences of GUDs in adults, showing declines of 1.5-2.5 orders of magnitude between the 1920s and the 1950s.

In the 1920s, many male immigrants entered the city, raising the sex ratio to 3.5:1, and encouraging commercial sex work (CSW). By 1928, 70% of women were considered "femmes libres" (promiscuous). In 1929-31, large surveys of most women of Leo-East uncovered that 5% had active genital ulcers.

Figure 5. Defining the "epochs" of GUD intensity in African cities. All countries passed similar phases. The transition times of the Belgian Congo are marked in the scale.

Pre-colonial epoch	Early colonial epoch	Nascent cities' epoch	Venereal control epoch	Penicillin epoch	Herpes epoch
- Large agglomerations far from forests - GUD absent in forest areas	- Colonial centers very small - GUD massive in centers	- Main city initial growth - Poor health system - GUD massive in cities	- Improved health systems, mass surveys and treatments - GUD less incident	- Cities continue to grow fast and surpass 10^6 inhabitants - Penicillin massively employed - GUD rare in cities	- Cities became huge - Herpes now pandemic and causing more genital ulcers than other GUDs.

Time → 1885 1918 1935 1947 1980

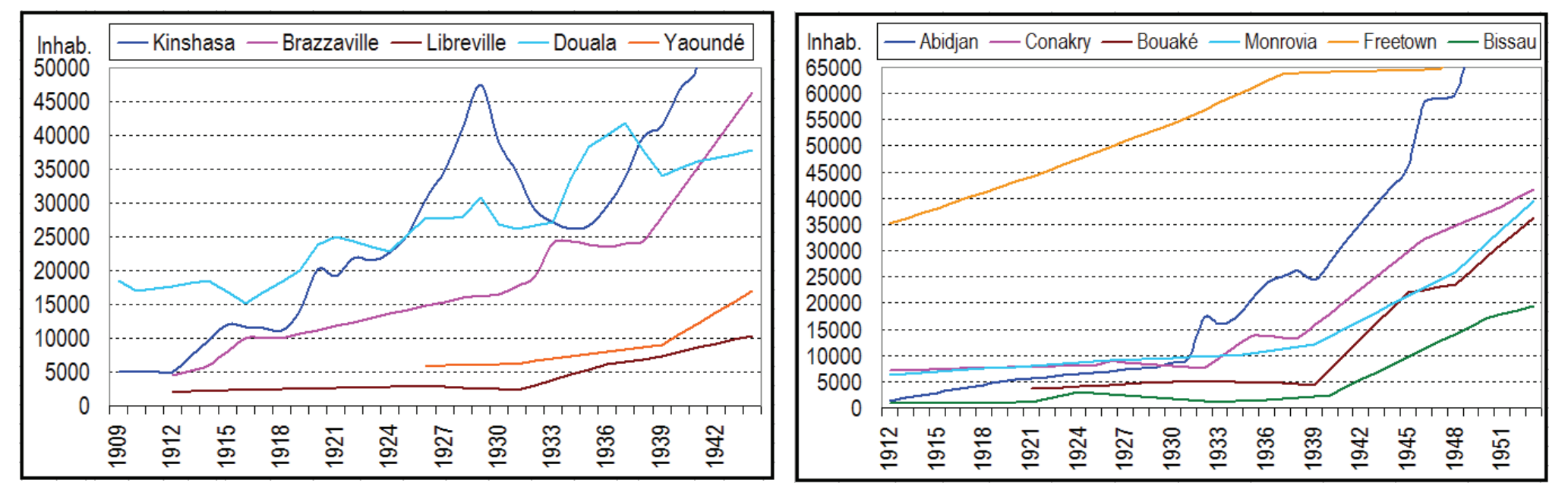

Figure 6. The growth of the most relevant cities at or near: chimpanzee and gorilla ranges in Central Africa (left); sooty mangabey range in West Africa (right).

Conclusions:

- Each city of the relevant areas had, in its earliest growth phase, GUD incidences 1.5-2.5 orders of magnitude higher than in later phases (figures 4 and 5).
- The earliest sharp growth periods of Kinshasa, Douala, and Abidjan, when these cities exceed 20,000 inhabitants, roughly coincide with TMRCA estimates of HIV-1-M, HIV-1-O, and HIV-2, respectively (figure 6), and these viruses spread earlier in their respective countries.
- A model centered in the driving factor of GUD in major cities explains better the timings of HIV emergence (table 1) than paradigmatic models (figure 2), potentially solving the Second Timing Paradox (part II).
- It may also explain why only two widespread HIV-1 groups emerged in Central Africa, i.e., this number becomes more than accidental.

Working hypotheses

Main Hypothesis

Each HIV group adapted better to humans, thanks to copious sexual transmission, in an African major city, at times of highly incident, uncontrolled GUD.

Rationale: GUD-related transmissibilities are high, and colonial cities had periods of very high GUD levels.

In addition, the hub of infectees generated in this way were uniquely well placed to spread the virus to the rest of the colony afterwards (which a small town would unlikely achieve).

Non-circumcision Hypothesis

The above described process needed a relatively low male circumcision rate to cause HIV emergence.

Rationale: Female→male per-act transmissibility from a GUD-suffering woman decuplies (from 4% to 43%), if the man is not circumcised (Part III); after transfusions, this is the highest transmissibility ever measured. SIVcpz and SIVsmm may be adapted to exploit their hosts' foreskins, and so more easily make the adaptive transition to humans in populations with foreskins.

Examining evidence

- The Main Hypothesis is consistent with the TMRCAs, as already stated; but it doesn't explain why HIV emerged in some countries and not in others.
- If circumcision practice was common in the capital cities of countries where HIV groups emerged, this would explain the country selection, and would support the Non-circumcision Hypothesis. We present this study in part IV.
- We built epidemiological simulations to test many scenarios, with different demography, GUD levels, and circumcision rates, thus testing our two hypotheses. We present these simulations in part V.

IV. Male circumcision in Central and West Africa

Methods

Literature reviewed

- Modern papers relating HIV prevalence and male circumcision
- Demographic and Health Surveys (DHS)[22]
- Revised Ethnographic Atlas, 1999[23]
- Primary ethnographic papers written in the period 1880-1960
- Tables of surgical operations in colonial medical reports

Coverage of all numerically important ethnic groups of the countries at or near chimpanzee, gorilla, and sooty mangabey ranges, including many lacking in the Ethnographic Atlas[23], and including non-ethnic groups (e.g., Creoles).

Information gathered

- Circumcision status, age of the operation, generality
- Temporal changes in circumcision practice
- Ethnic group distribution in the main cities for several time points
- Cases of phimosis and paraphimosis (which only affect non-circumcised males) from tables of surgeries

To compute estimates of circumcision frequency for cities, we used the criteria described in table 2.

Male circumcision practice as described in ethnographies	Estimated frequency at age 20
Culturally mandatory, up to puberty	95-98%
Culturally mandatory, and in many cases after puberty	85-95%
Present, but with many exceptions	50-70%
Absent	0-5%
Present, but consists of incisions and not removal of foreskin	0-5%
Adopted recently, and ethnographies provide approximate date of adoption	Starts at 0-10% and both limits raise linearly up to the present level

Table 2. Criteria for the upper and lower estimates of circumcision frequency in adults in ethnic groups.

Results

- Circumcision is now almost universal in all relevant countries, excepting Rwanda, Burundi, Uganda, and Tanzania. The rate is 93% in Cameroon, 95% in Côte d'Ivoire, and >97% in the other countries covered by DHS[22].
- However, at the time of most ethnographies studied (1900-1930), still many groups didn't practice it, and many had just adopted it, imitating other groups. Others adopted it in mid 20th century.

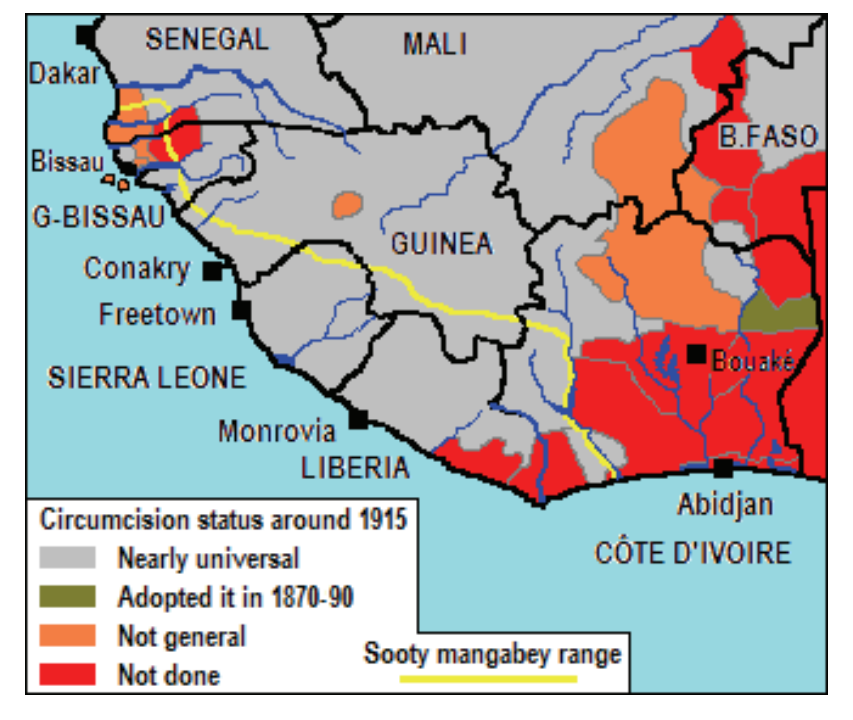

Figure 7. Distribution of male circumcision in West Africa circa 1915.

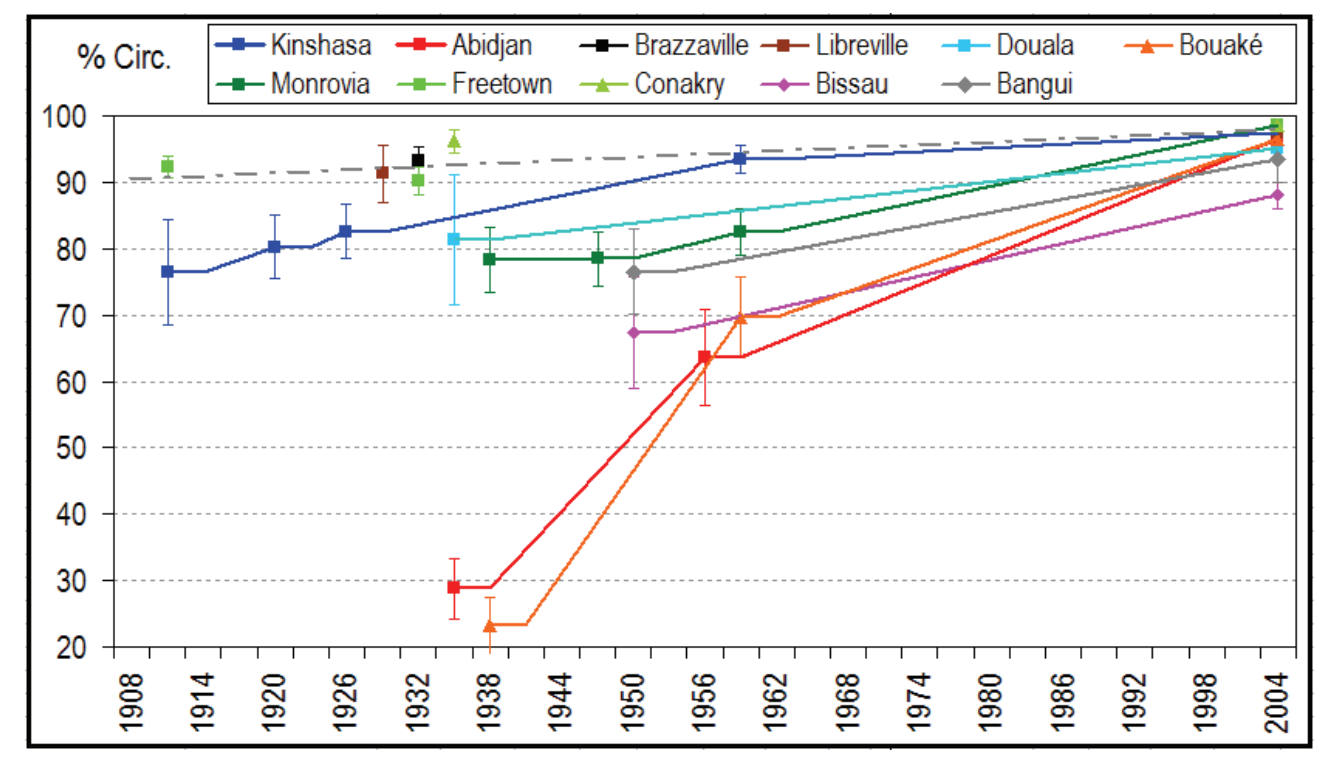

Figure 8. Estimates of circumcision frequency in males aged 20, based on tables of ethnic composition, and applying the criteria listed in table 2.

- Many of the cities seem to have had always >90% circumcision rate (dashed trendline).
- Kinshasa had clearly lower circumcision rate in the critical period (1910-35) than the other big Central African cities studied, (excepting Douala).
- Douala's high levels of phimosis (table 3) suggest many non-circumcised men.
- Abidjan and Bouaké (Côte d'Ivoire) were clear outliers in West Africa, with a majority of non-circumcised men.
- Monrovia and Bissau also had sizeable proportions of non-circumcised men; however they were very small and stagnant in the critical period (12,000 and 3,300 inhabitants around 1940, respectively).
- In Rwanda and Burundi, circumcision is uncommon; however their cities developed very late, and their main ethnic groups lack a tradition of bushmeat consumption.

Tracking phimosis and paraphimosis in cities

Table 3. Phimosis and paraphimosis cases, and their annual incidence in adult males.

Colony	City / division	Years	# cases	Ann.inc.
Belgian Congo	Leopoldville	1907,1910-12	74	0.685%
Belgian Congo	Leopoldville East	1926	46	0.357%
Belgian Congo	Leo, Matadi, Boma[a]	1930-31	245	0.395%
French Congo	Brazzaville	1930-34	89	0.265%
Cameroon	Douala / Wouri[b]	1932,1935	313	0.635%
Mali	Bamako	1937	4	0.045%
Senegal	Saint Louis	1937	6	0.040%

[a] The incidence is calculated over the joint adult male population of the 3 cities; about 3/5 of the operations were in Leo. [b] Most people from Wouri division were in Douala.

We gathered tables of surgical operations discriminating circumcisions for phimosis and paraphimosis, concentrating on major cities. Most cases should be in young adults or adolescents from the urban area or nearby. It's very difficult to translate these figures in estimates of circumcision, but they help to pinpoint regional differences. The low incidences of Mali and Senegal are explained by the Islamic practice of circumcision in childhood. This table suggests that Douala had even lower circumcision rate than Leopoldville or Brazzaville.

Conclusions:

- We found a geographical negative correlation, among countries, between HIV emergence and circumcision rates during the critical period (1910-35). The DRC, Cameroon, Côte d'Ivoire, and Guinea-Bissau (all early epicenters), and their main cities, had lower rates (figures 7 and 8).
- Among the cities which were already big, industrialized, and growing in the critical period, Kinshasa, Abidjan, and Douala, had lower rates than the others.
- Whether or not non-circumcision was necessary for HIV adaptation and emergence, this study may shed light on the early history of HIV groups; for example, within West Africa, Côte d'Ivoire and Guinea-Bissau had lower circumcision levels in mid century, and they were the exclusive epicenters of HIV-2 in the period 1960-1980[24].

V. Simulating the initial spread of HIV

Methods

We implemented a simple individual-based stochastic simulation of initial HIV epidemics. The model tracked the spread of the virus over a dynamical network of sexual contacts. Simulations were started with a single infected male. We focused on the initial spread of the virus (the first year), before it could fully adapt to efficient transmission in humans. The model considered the effect of GUD and circumcision status on HIV transmission. Transmission rates were scaled after estimates on modern HIV-1 (Table 4); transmission was restricted to acute infection. The sexual network consisted of stable (spousal) links, short-term links and male visits to CSW. The network was parameterized according to modern studies[25], with the exception of "femmes libres", whose promiscuity was adjusted to meet the "demand" of men for short-term links.

Situations	Per-act transmissibility
♂ → ♀ and ♀ → ♂(C)	0.001
♀ → ♂(NC)	0.0025
♂ → ♀(GU)	0.07[a]
♀(GU) → ♂(C)	0.04[b]
♀(GU) → ♂(NC)	0.43[b]
♀ → ♂(GU)	0.023[c]
♂(GU) → ♀(GU) and ♀(GU) → ♂(GU)	0.43

Table 4. Transmission rate estimates for chronic infection with modern HIV-1. "GU" indicates the presence of a genital ulcer and; "C" and "NC" indicate the circumcision status of the male. Acute infection lasts 12 weeks and is characterized by a 26-fold increased transmission potential[26]. Assuming lower initial efficiency for early HIV, in the simulations we set acute transmissibility rates using a 10-fold multiplier on the modern chronic rates (with a ceiling of 0.9).

[a] Supported by ref.16; [b] Supported by ref.17; [c] Applying the same multiplier for GUD in the exposed person measured in ref.16.

We considered four main scenarios to investigate why SIV could establish epidemics in humans in a short time window. Three scenarios involved Leopoldville/Kinshasa, which was the likely epicentre of HIV-1-M, and for which we have gathered extensive original data.

Pre-colonial village: A large settlement from the pre-HIV era, with balanced sex ratio, most sexually active adults married, no CSW, no GUD, and no circumcision.

Leopoldville 1919 and **1929**: These two scenarios were selected from the range estimated for the TMRCA of HIV-1-M by phylogenetic methods. Most data were available for 1929; 1919 was selected because it is closer to the most recent best estimate[11]. Both time points were characterized by rampant GUD epidemics, highly male-biased sex ratio and lower levels of circumcision than today.

Leopoldville 1958: A time point beyond the origin of HIV groups, with larger population, GUD under control and near universal circumcision.

Parameter		Pre-colonial village	Leopoldville		
			1919	1929	1958
Number of women		500	3265	10081	69159
Number of men		500	8798	31817	93064
% of women f.libres		0	60	60	10
% of men circumcised		0	70	80	95
Genital ulcer frequency* in %	CSWs	-	15	10	5
	Femmes libres	0	7.5	5	0.5
	Other women	0	3	2	0.3
	Men	0	1.5	1	0.3

Table 5. Scenario-specific parameters of the simulations, based on archival historical data[21].

* Frequency was kept constant by random replacement of recovered infections; the duration of GUD periods was 10 weeks.

Results

- Kinshasa around 1919-29 was uniquely permissive to the early spread of HIV with order: Kinshasa 1919 > Kinshasa 1929 >> Kinshasa 1958 >> pre-colonial village (figure 9).
- The initial zoonotic infection was a dead-end in most simulations. In the most permissive Kinshasa 1919 scenario, 10% of the simulations achieved at least 3 subsequent transmissions.
- Sensitivity analysis: we performed simulations varying key parameters of sexual promiscuity, transmission rate factors associated with acute infection and male circumcision, and the maximum transmission rate; we also tested allowing for chronic infection with current chronic transmissibility estimates. The relative permissivity of the 4 scenarios remained robust in all variants.
- GUD prevalence was the key factor for the early spread of HIV (figure 10).
- Circumcision prevalence had moderate effect, even comparing universal and no circumcision, or using a 10-fold factor for the transmission rate (figure 10).
- Large city size was not necessary for the initial spread of the virus (figure 10).

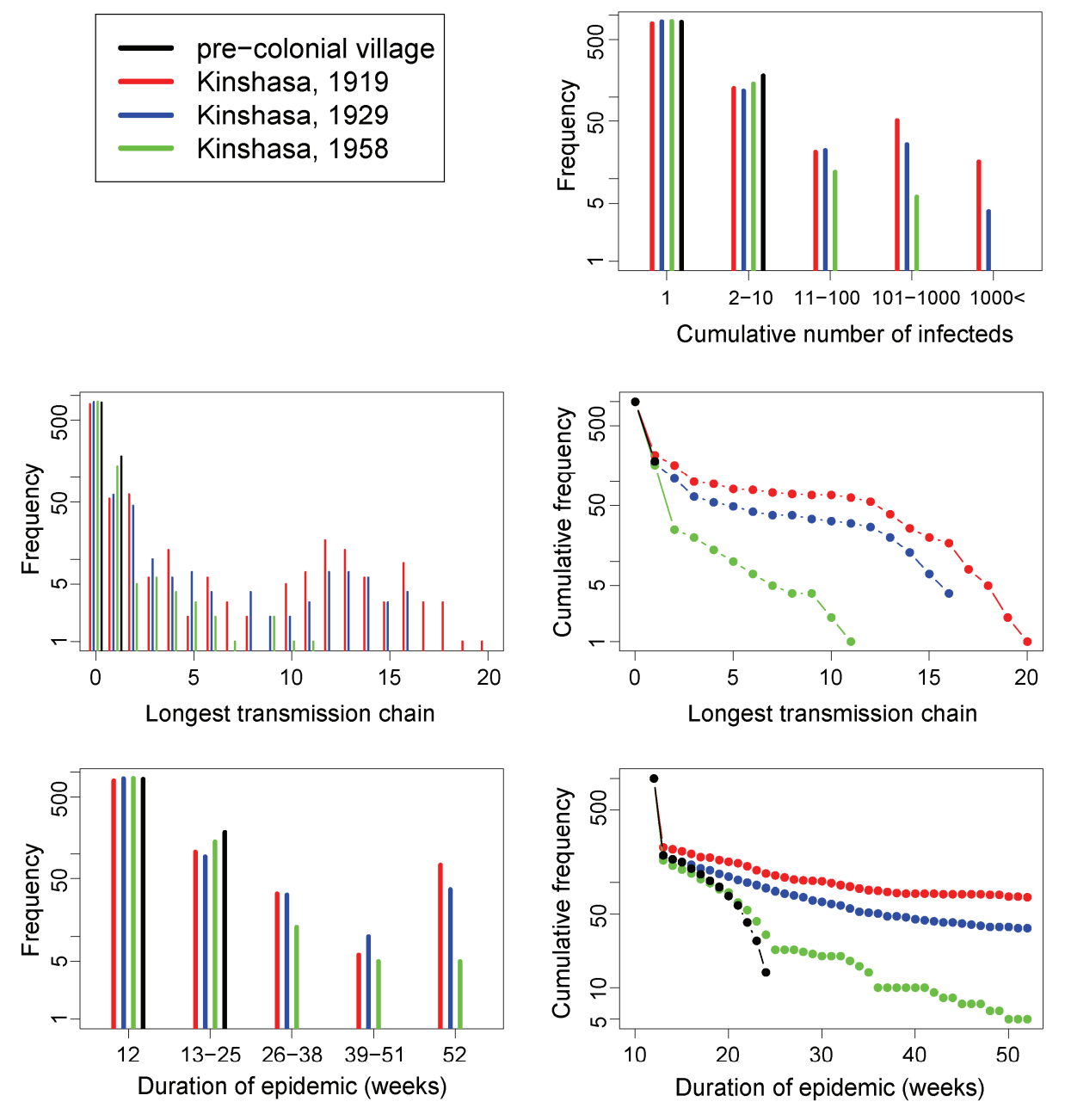

Figure 9. Comparison of the main scenarios: Kinshasa in 1919-29 was uniquely permissive for the spread of HIV.

Each scenario was simulated 1000 times, lasting a single year; the panels show counts of outcomes on a log scale. The success of an epidemic can be characterized by its duration (minimum 12 weeks: the length of the first acute infection) and the cumulative number of infecteds. In addition, the potential of the virus to adapt to humans was probably limited by the length of the longest transmission chain.

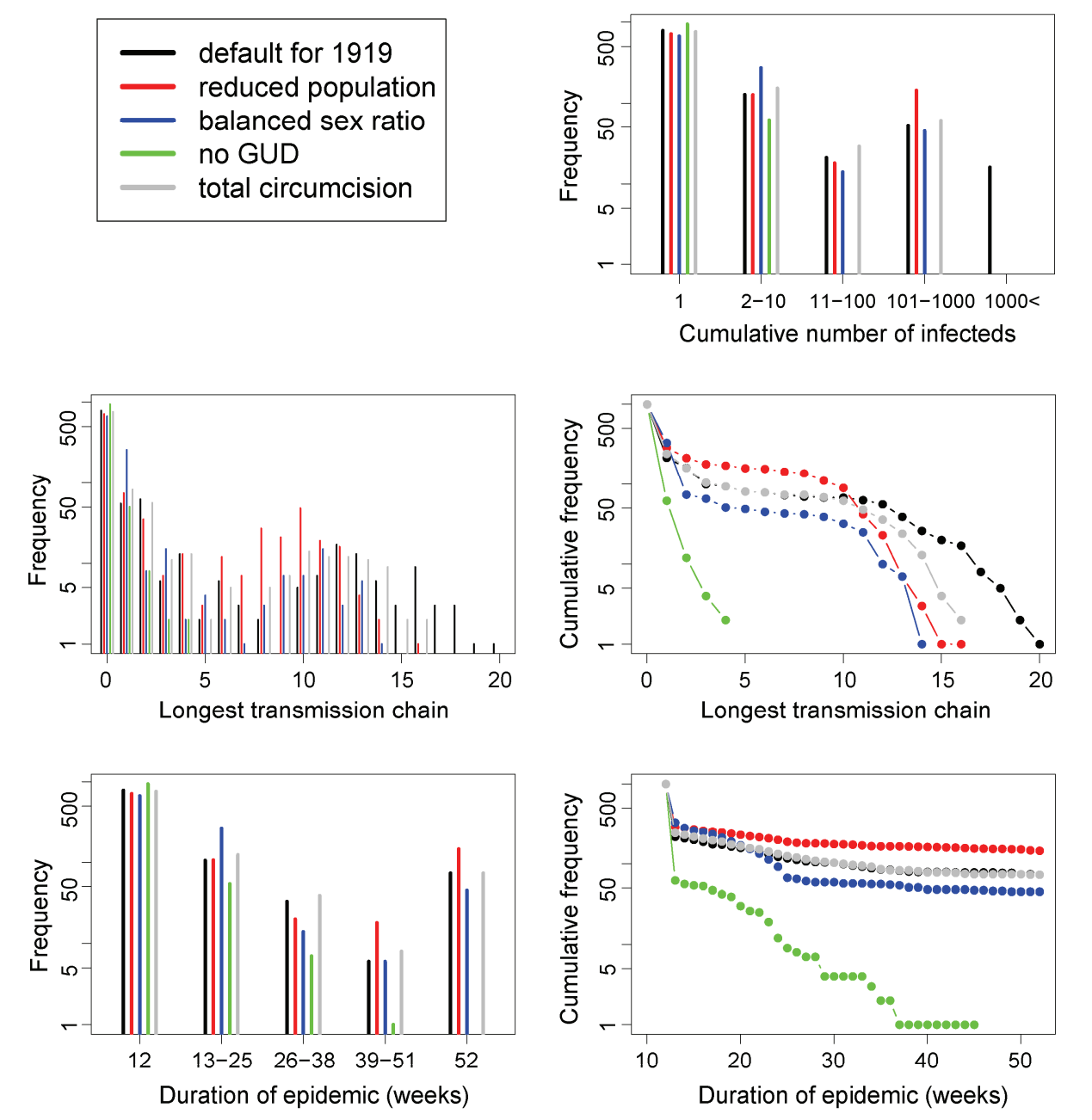

Figure 10. Variants to the Kinshasa 1919 scenario: GUD prevalence had the most dramatic effect.

To identify the key factors that facilitated the spread of HIV in 1919, we varied 4 factors to approach the non-permissive scenarios: 10-fold reduced population, balanced sex ratio (with 90% married), no GUD and universal circumcision.

Conclusions:

The simulations confirmed that the period around 1919-29 was uniquely permissive for the early spread of HIV. In the model, the single most important direct effect was rampant GUD. We therefore conclude that the possible impact of non-circumcision on HIV origins (apparent in the geographical pattern presented in part IV) was probably mediated partly by its indirect effect on GUD prevalence. Large city size was not important. Colonial disruption of population structure and high promiscuity opened the time window for successful SIV zoonoses by fuelling GUD epidemics, and the window was closed by efficient medical STD control, in spite of continuing population growth and decreasing but still high promiscuity.

General Conclusions

Time coincidence

- GUD incidences in nascent colonial cities were orders of magnitude higher than in mid 20th century (part III). The critical GUD period fits the start of HIV spread better than injection intensity or urbanization.
- Moreover, the earliest periods of sharp growth of Douala (1916-21), Kinshasa (1918-29), and Abidjan (1931-45), closely match the TMRCAs of HIV-1-O, HIV-1-M, and HIV-2, respectively (table 1; figure 6).

Theoretical viability

- Unlike models emphasizing parenteral serial transmission[4], our GUD hypothesis is more compatible with gradual adaptive evolution to exploit the human genital tract.
- Our simulations, based on published transmissibility measurements, show the viability of this process, for the GUD levels existing in the critical epoch (part V).
- Our model does not disavow the notion of a parenteral chain having provided initial rough adaptation.
- The simulations suggest that small towns / settlements could initiate the process as well as big cities.
- Still, fast-growing major cities received more SIV infectees per year, and were uniquely well placed to spawn an emergent virus to the rest of the colony, thanks to their privileged connections. This explains why the epidemically successful HIV groups are few.

Geographical correlations

- Among the cities which were large and growing in the critical period, Kinshasa, Douala, and Abidjan, had lower circumcision rates. However, our simulations don't conclude that the 70-80% rate of Kinshasa (vs >90% in most others) was instrumental in HIV-1-M emergence.
- On the contrary, in West Africa, Ivorian cities are singular in their very low circumcision rates. Two HIV-2 groups evolved in Côte d'Ivoire and none did it in the other countries. Thus non-circumcision may have been more important for HIV-2 evolution.

Acknowledgments

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