Predicting the unpredictable: Transmission of drug-resistant HIV

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We use a mathematical model to understand (from 1996 to 2001) and to predict (from 2001 to 2005) the evolution of the epidemic of drug-resistant HIV in San Francisco. We predict the evolutionary trajectories for 1,000 different drug-resistant strains with each strain having a different fitness relative to a drug-sensitive strain. We calculate that the current prevalence of resistance is high, and predict it will continue to rise. In contrast, we calculate that transmission of resistance is currently low, and predict it will remain low. We show that the epidemic of resistance is being generated mainly by the conversion of drug-sensitive cases to drug-resistant cases, and not by the transmission of resistant strains. We also show that transmission of resistant strains has not increased the overall number of new HIV infections. Our results indicate that transmission of resistant strains is, and will remain, a relatively minor public health problem.

A major public health concern is that a 'new' epidemic generated by sexually transmitted drug-resistant strains of HIV would arise if combination antiretroviral (ARV) therapies were widely deployed in developing countries. This expectation is based upon experience with other pathogens (such as *Mycobacterium tuberculosis*) where, in certain locations, drug-resistant strains have increased the death rate[1]. Epidemics of drug-sensitive and drug-resistant pathogens have fundamentally different dynamics. Epidemics of drug-sensitive pathogens are generated only by transmission. However, epidemics of drug-resistant pathogens are generated by two sources: at-risk uninfected individuals (infected by transmission of drug-resistant strains), and treated individuals (who were initially infected with drug-sensitive strains, but acquire drug resistance during treatment)[2–5]. Hence, epidemics of drug-resistant pathogens have the potential to rapidly increase to substantial levels[3,4]. Combination ARV therapies that involve three or more anti-HIV medications (typically a protease inhibitor, or a non-nucleoside reverse transcriptase inhibitor with at least two nucleoside reverse transcriptase inhibitors) have been widely used in San Francisco since 1996 (ref. 6). These therapies have substantially reduced the AIDS death rate in this city[7] and elsewhere[8–11]. However, ARV-resistant strains have emerged and have been sexually transmitted[12–15] (ARV resistance is defined as lost suppression of viral replication to a three-drug regimen). Here, we calculate the degree of transmission of ARV-resistant strains that has occurred in San Francisco since 1996, and we predict the expected transmission rates through 2005. We also quantify the contribution of transmitted resistance in advancing the epidemic of ARV resistance and identify the key factors driving transmitted resistance. Finally, we use our results to identify effective strategies for reducing ARV resistance in San Francisco and the developing world.

We predicted the transmission of ARV-resistant strains in the gay community in San Francisco from 1996 to 2005 by using an uncertainty analysis, based upon a Monte Carlo sampling scheme (see Methods) to generate predictions from a mathematical model[16]. The model generates cases of acquired ARV resistance at a certain rate that is a time-dependent function of the number of infected drug-sensitive cases, the treatment rate (with ARV) and the rate at which ARV-resistant strains emerge during treatment[16]. Cases of acquired ARV resistance can then transmit ARV-resistant strains to at-risk uninfected individuals[16]. We predicted the transmission potential of 1,000 different ARV-resistant strains. As the fitness of ARV-resistant strains is uncertain, we varied the relative fitness (as specified by the transmissibility of the ARV strain relative to that of a drug-sensitive strain) of the 1,000 strains over a wide range; we assumed that an ARV-resistant strain could range from being almost as transmissible (maximum relative fitness) to only 1% as transmissible (minimum relative fitness) as the drug-sensitive strain. We included an uncertain degree of increase in risky behavior[16], as rates of risky sexual behavior have been increasing in San Francisco[17–19]. We assumed that risky behavior could increase anywhere from no increase (so that risky behavior maintained the current prevalence of HIV at 30%)[6] to double the current level[16]. We also included uncertainty in the rate of development of acquired resistance (that is, the direct conversion of drug-sensitive cases into ARV-resistant cases during treatment) by assuming that ARV resistance could emerge in 10–60% of treated drug-sensitive cases per year[16]. This range is based upon recent data from clinical and community-level studies of ARV resistance[20–28]. We assumed that 50–90% of HIV-infected gay men would take ARV (ref. 16). Although treatment rates are high[6,16], the exact value of the treatment rate in San Francisco is unknown.

Prevalence of ARV resistance

Our predictions revealed the temporal changes in the competitive dynamics between the drug-sensitive and the ARV-resistant strains at the epidemic level (Fig. 1). The predicted effect of different treatment rates (ranging from 50–90%) on the prevalence of drug-sensitive and ARV-resistant infections is shown for 1997 (Fig. 1*a*), 2000 (Fig. 1*b*) and 2005 (Fig. 1*c*). High treatment rates significantly decreased the percentage of

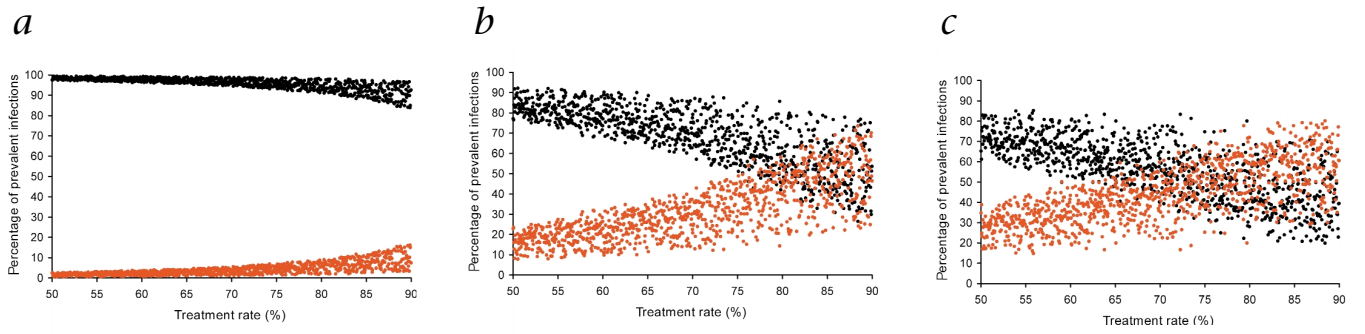

Fig. 1 Predictions calculated using model described previously[16] and time-dependent uncertainty analyses[29,30]. ***a–c***, Predictions show the temporal impact of the treatment rate (in terms of the percentage of drug-sensitive cases receiving treatment) on the prevalence of drug-sensitive infections (black data) and the prevalence of ARV-resistant infections (red data) in San Francisco. ***a***, ***b***, and ***c*** correspond to 1997, 2000 and 2005, respectively; median values for the prevalence of ARV-resistant infections shown here are 3.3% (*a*; 1997), 28.5% (*b*; 2000) and 42.2% (*c*; 2005).

drug-sensitive infections, but substantially increased the percentage of ARV-resistant infections (Fig. 1). By the year 2000, 28.5% (median value, Fig. 1*b*) of the prevalent HIV infections in San Francisco were ARV-resistant. Our prevalence estimate is in close agreement with the limited (n = 50) available clinical data that indicate that 28% of prevalent cases at San Francisco General Hospital in 1999 were ARV-resistant to at least a single anti-HIV medication (M. Roland, pers. comm.). Sensitivity analysis[29,30] of our predicted data revealed that three key factors increased the prevalence of ARV resistance (Table 1). These factors were the treatment rate (Fig. 1), the average duration of time that an ARV-resistant patient spent on ineffective therapy, and the rate of development of acquired resistance. High rates of development of acquired resistance caused a high prevalence of ARV resistance (Fig. 2), and this effect increased with time (Fig. 2). However, even a fairly low rate of development of acquired resistance (for example, 20% of cases per year) caused a high percentage (10–40%) of ARV resistance among the prevalent infections by 2000 (Fig. 2). Our predictions revealed that the prevalence of ARV resistance (and hence the clinical burden of ARV resistance) is already high in San Francisco, and will continue to increase substantially through 2005 (Fig. 2).

Temporal dynamics of transmission of ARV-resistant strains

Our predictions for the temporal dynamics of transmitted resistance in San Francisco are shown graphically in terms of the percentage of the new HIV infections (that is, incident infections) that are ARV-resistant (Fig. 3*a*). We also present explicitly our quantitative estimates (median, interquartile range, maximum and minimum) for these predictions (Table 2). Transmitted resistance accounted for only a relatively small proportion of the new infections that have occurred; in the future, the vast majority of new infections each year will be drug-sensitive (Fig. 3*a*, Table 2). For example, we estimated that in 1999 only a few (median, 6.5%; interquartile range, 2.2–13.2%) of the new infections were ARV-resistant (Fig. 3*a*, Table 2). The median value of our estimate of the transmission rate of ARV resistance in 1999 is in very close agreement with observed genetic marker data (Fig. 3*a*), which show resistance to non-nucleoside reverse transcriptase inhibitors and protease inhibitors in recently-infected treatment-naive patients was 6% in 1999 at San Francisco General Hospital (R. Grant, pers. comm.). Transmitted resistance is likely to increase only gradually (Fig. 3*a*, Table 2) with a current doubling time of approximately four years. Thus, even by 2005 only a relatively low percentage (median, 15.6%; interquartile range, 6.1–28.1%) of the new infections are likely to

Table 1 Key factors that increase (PRCC > 0) or decrease (PRCC < 0) the prevalence and transmission of ARV resistance

	Key factors driving the prevalence of ARV resistance		Key factors driving the transmission of ARV resistance	
Key factor	Value of PRCC at year 5	Value of PRCC at year 10	Value of PRCC at year 5	Value of PRCC at year 10
Treatment rate[a]	0.96	0.92	0.89	0.87
Rate of development of acquired resistance[b]	0.92	0.86	0.64	0.51
Average length of time a case with ARV-resistant strains remains on ineffective treatment	0.48	0.70		
Relative fitness of ARV-resistant strain[c]			0.92	0.92
Transmissibility of drug-sensitive strains from treated patients			–0.49	–0.60

[a],Defined as percent of drug-sensitive cases receiving ARV. [b], Defined as % of treated drug sensitive cases that develop ARV resistance per year. [c], Defined as the transmissibility of an ARV-resistant strain relative to the transmissibility of a drug-sensitive strain. PRCC, partial rank correlation coefficient.

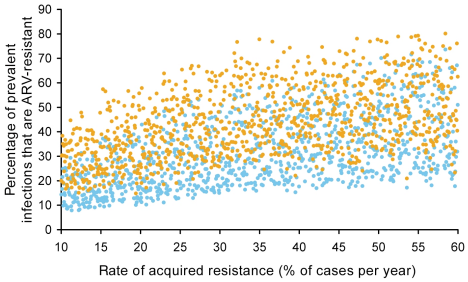

Fig. 2 The rate of acquired resistance is a key factor in determining the prevalence of ARV resistance. Results using unadjusted predicted data from the model for 2000 (turquoise data) and 2005 (orange data); each datum represents one of the 1,000 simulations. The scatterplot shows the effect of the rate of acquired resistance (in terms of percentage of treated drug-sensitive cases per year developing acquired resistance) on increasing the prevalence of ARV resistance in San Francisco.

be ARV-resistant (Fig. 3*a*, Table 2). The majority (median, 84.4%; interquartile range, 71.9–93.9%) of the new infections in 2005 will be drug-sensitive. However, our predictions have revealed that it is possible (but unlikely) for extremely high rates of transmitted resistance to occur (Fig. 3*a*, Table 2).

We then used our predictions to calculate the relative contribution of transmitted resistance versus the development of acquired resistance in driving the epidemic of ARV resistance. The vast majority of new cases of ARV resistance were the result of acquired resistance (Fig. 3*b*). Transmitted resistance only accounted for a relatively small percentage of the new cases of ARV resistance that occurred each year. For example, we determined that in 2000, most (median, 92%; interquartile range, 86.3–96.8%) of the new cases of ARV resistance were due to acquired resistance, and that few (median, 8%; interquartile range, 3.2–13.7%) of these cases were due to transmission of resistant strains (Fig. 3*b*). Even by 2005, still only a few (median, 14%; interquartile range, 6.1–21.2%) of the new ARV-resistant cases will result from transmitted resistance (Fig. 3*b*).

Key factors in driving the transmission of ARV resistance

We identified four key factors (Table 1) that increased the transmission of resistance: 1) increasing treatment rates (Fig. 3*c*); 2) increasing rates of acquired resistance; 3) increasing relative fitness of the ARV-resistant strain that generated the epidemic (Fig. 3*d*); and 4) decreasing transmissibility of the drug-sensitive strains from treated patients (in the model, this factor reflects the degree of treatment-induced reduction in viral load[16], which reduces transmissibility as indicated by empirical studies[31]). We used our predicted data to quantify the relationship between the treatment rate and transmitted resistance (Fig. 3*c*). If 50–70% of infected cases were treated, then 30% or less of the new infections in 2000 were ARV-resistant (Fig. 3*c*). However, if the treatment rate was extremely high (for example, if 85–90% of infected cases were treated) then up to 70% of the new infections in 2000 were ARV-resistant (Fig. 3*c*). We also used our predicted data to quantify the relationship between a second key factor (the relative fitness of the ARV-resistant strain) and transmitted resistance (Fig. 3*d*). ARV-resistant strains that had a high relative fitness in treated patients generated a high transmission rate (Fig. 3*d*). The relative fitness of ARV-resistant strains in treated patients depended on two factors: the intrinsic fitness of the ARV-resistant strain, and the degree to which the therapies could effectively decrease viral load (and hence reduce transmissibility[31]). Thus, the high transmission rates (Fig. 3*d*) occurred because the ARV-resistant strain was very intrinsically fit (that is, highly transmissible) and/or the ARV-resistant strain occurred in patients that had insufficient viral suppression due to the treatment regimen.

Cumulative number of HIV infections prevented

Increases in risky sexual behavior have increased the annual number of new HIV infections in San Francisco[7]. To determine whether transmitted resistance has led to an additional increase in the annual incidence rate, we adjusted our predicted data for increases in risky behavior (Fig. 4). Our analysis showed that if risky behavior had not increased, the number of new infections would be decreasing, even though ARV-resistant strains are being transmitted (Fig. 4). Hence, transmitted resistance has not increased—and our predictions reveal that it will not increase—the

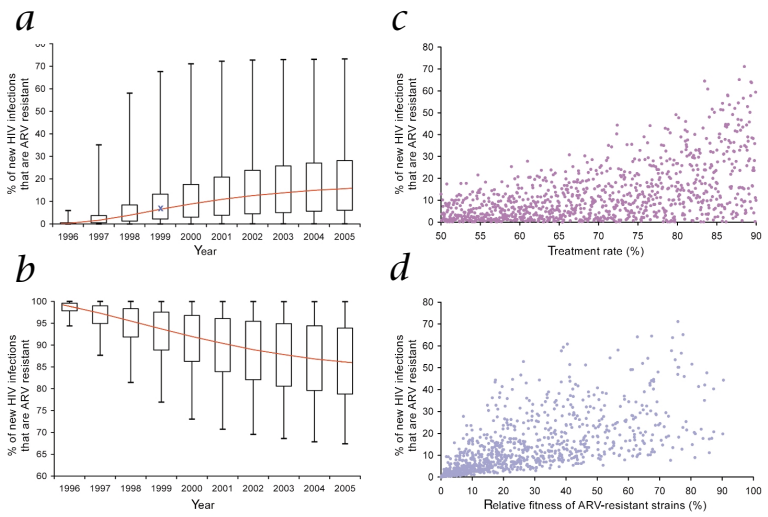

Fig. 3 Temporal predictions for transmitted resistance ***a***, Temporal predictions calculated using model previously described[16] and time-dependent uncertainty analyses[29,30] showing the predicted transmission of ARV-resistant strains in San Francisco from 1996 to 2005. Each year the 1,000 simulations are plotted as a box-plot; these plots show the median value (red line), upper and lower quartiles and the outlier cutoffs. ×, the blue datum is calculated from empirical data collected in 1999 from recently-infected treatment-naive patients. ***b***, Predictions showing the annual contribution of acquired resistance to the number of new cases of ARV resistance in San Francisco over time. Red line shows the median values. ***c***, Results using unadjusted predicted transmission data from the uncertainty analysis for the year 2000; each datum represents one of the 1,000 simulations. Scatterplot shows the effect of the treatment rate on increasing the transmission of ARV-resistant strains (in terms of the percentage of new HIV infections that are ARV-resistant) in San Francisco. ***d***, Scatterplot shows the effect of the relative fitness of ARV-resistant strains on increasing the transmission of ARV-resistant strains (in terms of the percentage of new HIV infections that are ARV-resistant) in the year 2000. Fitness (as specified by transmissibility) is plotted relative to the fitness of drug-sensitive strains. Each datum represents one of the 1,000 different ARV-resistant strains.

Table 2 Temporal predictions of the transmission of ARV-resistant strains in terms of percentage of new HIV infections that are ARV-resistant

Year	Median value	Interquartile range	Minimum value	Maximum value
1996	0.25	0.08–0.56	0.0008	5.90
1997	1.60	0.53–3.72	0.005	35.09
1998	3.88	1.27–8.42	0.01	58.09
1999	6.48	2.18–13.21	0.02	67.65
2000	8.89	3.02–17.53	0.03	71.07
2001	10.90	3.88–20.80	0.03	72.27
2002	12.55	4.54–23.80	0.04	72.72
2003	13.81	5.05–25.74	0.04	72.93
2004	14.93	5.68–27.05	0.04	73.08
2005	15.64	6.05–28.10	0.05	73.21

annual incidence rate in San Francisco (Fig. 4). After adjusting for increasing risky behavior, we estimate that the high treatment rate in San Francisco has significantly reduced transmission; by 2005 approximately one HIV infection will have been prevented for each prevalent case of ARV-resistance (Fig. 4). As the prevalence of ARV resistance will be high in 2005 (Fig. 1*c*), the cumulative number of infections prevented will be substantial.

Discussion

At this stage in the epidemic, it is difficult to predict the transmission rate of ARV resistance because little is known about the fitness of any ARV-resistant strains either *in vitro* or *in vivo*. Therefore, we predicted the evolution of the epidemic of ARV resistance by theoretically constructing (using a wide range of fitness values) 1,000 different strains of ARV resistance. Our analyses show that high usage of therapies will lead to a high prevalence of ARV resistance; these predictions agree with a recent report that shows significant increases in the prevalence of ARV resistance in North America[32]. Our analyses also show that even a high usage of therapies—for a wide range of fitness values for ARV-resistant strains—will lead to only a relatively low transmission of resistance. However, it is possible, if extremely fit ARV-resistant strains emerge, for high transmission rates of ARV resistance to occur. In the future, our theoretical predictions could be tested against empirical data of temporal trends of ARV resistance when relevant data are available. More studies (such as that of Stoddart *et al.*[33]) are necessary to measure the fitness of ARV-resistant strains *in vivo* and *in vitro*, as well as to assess their clinical significance.

Based on the results from our sensitivity analysis, we suggest four strategies to minimize the transmission and prevalence of ARV resistance. First, therapy should be delayed as long as possible. Delaying therapy reduces the treatment rate, which we have shown will slow the increase in the prevalence and the transmission of ARV resistance. Our recommendation supports the British[34] and the United States treatment guidelines (www.hivatis.org/guidelines/adult/April23_01/p.d.f..AAAPR23S) that recommend delaying therapy to maximize clinical benefit and to reduce clinical toxicities. Second, to reduce the rate of development of acquired resistance as much as possible, it is essential to prevent 'poor' treatment programs. It is unethical to withhold treatment based upon anticipated adherence, and screening for adherence has been shown to be inadequate for guiding therapy[35]. Hence, we suggest that clinical centers of excellence for HIV/AIDS treatment programs should be created to ensure a minimum rate of acquired resistance. Third, to more completely suppress resistant isolates, it is essential to develop therapies more effective for treating patients with ARV-resistant strains. Paradoxically, our results show that therapies which are extremely effective at suppressing drug-sensitive isolates will lead to increases in transmitted resistance. Fourth, the average length of time that an ARV-resistant case is receiving ineffective treatment should be minimized. All four strategies should be used in an overall program to reduce ARV resistance. San Francisco was an initial site of the HIV epidemic, and combination ARV therapies have contributed substantially to reducing disease progression rates[7], lowering the AIDS death rate[7,16] and reducing transmission[16]. Here, we have analyzed the epidemic-level effects that occur as a result of the evolution of the epidemic of ARV resistance. Based on our data, we present the following conclusions: 1) high treatment rates quickly led to a high prevalence of ARV resistance; 2) the prevalence of ARV resistance will continue to rise as a result of a high usage of these therapies; 3) the ARV resistance epidemic is being driven mainly by the conversion of drug-sensitive cases to ARV-resistant cases, and not by transmitted resistance; 4) transmitted resistance is currently low and is likely to only gradually increase; 5) transmitted resistance has not increased the overall number of new infections; and 6) the continual transmission of drug-sensitive strains is a substantially greater public health problem than the transmission of drug-resistant strains. Hence, our results indicate that transmitted resistance will be only a minor public health problem in San Francisco. Greater attention should be focused on preventing acquired resistance and on reducing the transmission of drug-sensitive strains. However, our predictions do indicate that transmitted resistance will soon present a significant clinical problem in San Francisco, because it will limit therapeutic options for a significant number of patients and necessitate drug susceptibility testing for all newly infected patients.

There is currently a debate as to whether combination ARV therapies should be widely used in African and other developing countries. It is still unclear whether the widespread use of these therapies would be logistically possible or economically feasible. An HIV vaccine would be the most effective way to control the HIV pandemic[36], but none are yet available. Based on our analyses for San Francisco, we advocate the expanded use of ARV in developing countries, but stress that therapies should be carefully used and coupled with effective risk-reduction interventions[37]. The same four strategies that we have suggested for

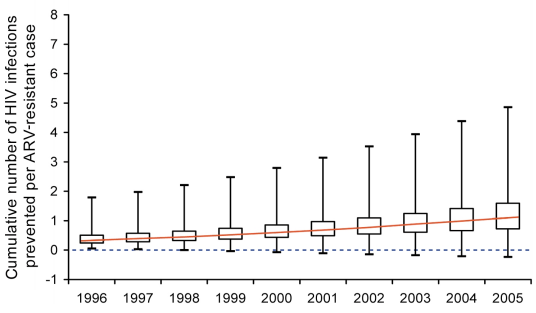

Fig. 4 Results of a 'biological cost-benefit' analysis of the epidemiological impact of combination ARV therapies in San Francisco, where 'benefits' are defined as the cumulative number of HIV infections prevented, and the 'costs' are defined in terms of a prevalent case of ARV resistance.

minimizing ARV resistance in San Francisco should also be used in developing countries. In particular, as these therapies are deployed, the prevalence and the transmission of ARV resistance should be monitored. Our results indicate that ARV resistance is likely to reach a high prevalence in developing countries, and that these epidemics of ARV resistance will be driven by acquired resistance and not by transmitted resistance. Our results also indicate that transmitted resistance is unlikely to increase the overall transmission rate in developing countries. The impact of combination ARV therapies on HIV epidemics is complex; our analyses clearly show that it is essential to treat, but it is essential to treat well.

Methods

The mathematical model is specified by five ordinary differential equations and has been described in detail elsewhere[16]; ARV-resistant cases can be superinfected with both drug-sensitive and ARV-resistant strains[16]. A web version of the model can be run at www.biomath.ucla.edu/faculty/sblower. Previously, we used this model to predict two different epidemiological futures (based upon 'optimistic' and 'pessimistic' assumptions) for San Francisco[16]. Each parameter in the model was assigned a probability density functions (p.d.f.); optimistic and pessimistic futures used different p.d.f.'s (ref. 16). To generate predictions for the prevalence and transmission of ARV resistance we used the same p.d.f.'s that had been used to generate the pessimistic future[16], because the pessimistic assumptions have since proved to be the most realistic assumptions[7]. All p.d.f.'s have been described[16]. Latin Hypercube Sampling was used to randomly sample (without replacement) the p.d.f. of each of the parameters in the model 1,000 times. This procedure produced 1,000 different parameter sets that were then used to numerically simulate the model; thus 1,000 different predictions were generated.

To identify the key factors that drive the prevalence and transmission of ARV resistance, we used our predicted temporal data to calculate time-dependent sensitivity coefficients. A partial rank correlation coefficient (PRCC)[29] was calculated annually for each parameter in the model[30]. A parameter was identified as a key factor if the value of the absolute value of the PRCC was greater than 0.5 anytime in the time period 1996–2005. Before calculating PRCCs, we examined scatterplots of each model parameter versus each of the two predicted outcome variables (prevalence and transmission of ARV resistance) at each year to check for monotonicity and discontinuities[29,38,39]. All relationships in the scatterplots were non-linear and monotonic; no interactions and no discontinuities were observed.

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