AIDS and COVID: A tale of two pandemics and the role of statisticians

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The world has experienced three global pandemics over the last half-century: HIV/AIDS, H1N1, and COVID-19. HIV/AIDS and COVID-19 are still with us and have wrought extensive havoc worldwide. There are many differences between these two infections and their global impacts, but one thing they have in common is the mobilization of scientific resources to both understand the infection and develop ways to combat it. As was the case with HIV, statisticians have been in the forefront of scientists working to understand transmission dynamics and the natural history of infection, determine prognostic factors for severe disease, and develop optimal study designs to assess therapeutics and vaccines.

KEYWORDS
AIDS, COVID-19, diagnostic testing, infectious disease modeling, pandemic

Almost 40 years after the reports of the first AIDS cases appeared,1 a new virus, SARS-CoV-2, has demanded the attention of the scientific community. Because it was very quickly obvious that the spread of this virus was global, was readily transmitted and affected nearly every aspect of modern life all over the world, that focus has been particularly intense. This is as true for the statistical community as for other areas of science; we have never been as singularly focused on an issue as on the global coronavirus pandemic. With so much unknown about this virus—ease, mode, and timing of transmission, sequelae of infection, mortality rate, host factors associated with infectivity and course of disease, methods of treatment, postinfection immunity—statisticians with expertise in multiple areas have turned their attention to these issues.

1 | MODELING THE OUTBREAK

Classical infectious disease models utilize differential equations to model the dynamics of disease spread in a homogeneous setting. The most basic of such models is the susceptible-infectious-recovered model, whose origin dates back to 1927.2 Such models require estimates of the size of the susceptible population, the likelihood of infection given exposure, and the size of the population recovered from the infection (who are presumably then immune to further infection). A refinement of this model, the “SEIR” model allows for an “exposed” population that may be infected but not yet capable of transmitting the infection.3 A range of estimates for these parameters will give us a range of possible magnitudes of the outbreak.

Such models were not relevant to the HIV pandemic, as there was no “recovered” population and hence no issue of immunity. Statisticians developed other models looking at issues like spread in different populations (homosexual,
For COVID-19, many statisticians and epidemiologists have been intensively engaged in pandemic modeling since the outbreak began early in 2020. Although much has been learned over the past months, our understanding of disease transmission and our ability to predict the course of the pandemic remains limited. Because transmission of the virus is airborne rather than through exchange of bodily fluids, virtually everyone is at risk of infection, making the identification and estimation of risk parameters much more complex.

SARS-CoV-2 follows the more typical outbreak pattern, and thus most of the models used to predict the scope of the outbreak have used standard modeling techniques for infectious disease outbreaks. Models, of course, rely on assumptions, and in early January 2020, when information about a new viral disease first emerged in China, very little information was available on which to base transmission models. The novelty of the virus led to some incorrect assumptions, for example, suggestions that SARS-CoV-2 would follow seasonal influenza patterns, and that viral transmission might essentially cease once the weather warmed up in the summer. In addition, basic theoretical models of infectious disease spread do not account for the variable environmental and community-level effects and interventions such as mask-wearing and social distancing protocols that strongly impact spread, so more advanced models were required to account for these factors.

As more information about transmission dynamics has been accrued, modelers have extended the basic models to account for factors such as heterogeneity of societal conditions and behaviors (contacts in the household, school, workplace, and community), local population characteristics, behavioral and governmental interventions, weather, and geographical factors, as well as detailed assumptions about disease transmission dynamics. The Institute for Health Metrics and Evaluation has taken a radically different approach. Rather than utilizing generative SEIR-type models, they fit nonlinear mixed-effects models to cumulative COVID-19-related death counts, incorporating various community mitigation strategies as predictors. This model became controversial due to its dramatically changing projections over time, wide uncertainty bounds, and the fact that it did not model any of the known infectious disease dynamics including exposure, transmission, and incubation periods that have been the staple of epidemiological infectious disease modeling for many years.

Many other types of models have been developed. Some have applied deep learning techniques, or hierarchical nonlinear mixed effect models, and have incorporated factors such as temperature, population density, day of week/time of day, and travel/commuting patterns, with models aimed at predicting cases, hospitalizations, or mortality rates. Given the proliferation of so many projection models for COVID-19-based mortality, some sites have aggregated these mortality forecasts across models to show them all in one place.

Models are continually adapting to new data. An important challenge has been the lack of consistency in reporting COVID-19 cases. Different types of tests granted “Emergency Use Authorization (EUA)” by the U.S Food and Drug Administration (FDA) are available, for example, polymerase chain reaction (PCR) mRNA-based tests, antigen tests, and serum-based antibody tests. Some states have counted only those with positive viral (PCR mRNA-based) tests, but others have also included antigen tests, that yield faster results but are considered less definitive, in their case counts. Recently, the FDA has communicated that, in general, antigen tests are less accurate than PCR-based molecular tests.

Finally, most asymptomatic cases have not been identified, as testing protocols in most places call for testing only those with symptoms or with known recent exposure to a confirmed case. As a result, confirmed case counts likely substantially underestimate community infection rates because of inadequate testing and false negative results; studies have yielded estimates ranging from 3 to 24 undetected infections for every confirmed case, or between 3 and 20.

Given these factors, test positivity rate has become an important measure to calibrate interpretation of confirmed case counts. If an increase in confirmed cases were solely due to an increase in testing, then the testing positivity rate would tend to remain stable or decline, while during an outbreak the test positivity rate would tend to increase, serving as a potential leading-edge indicator of viral surge. Alternatively, high test positivity rates, on the other hand, could indicate that a community is testing too few individuals, so that the confirmed case counts may severely underrepresent the community infection levels. The interpretation needs to account for the testing practices in the local community—for example, how much testing is done, what proportion of the infected population is tested, and whether cluster testing is done on high-risk cohorts such as nursing homes or meat packing plants.
Test positivity rate also depends on accurate testing data, which at times has been a challenge. Some testing labs reported positive but not negative cases, for example. There have been major delays in reporting test results, as well as conflation of serology (antibody) and viral (PCR) tests, and inconsistent reporting of antigen test data. The COVID tracking project has assembled the most complete set of testing data and includes documentation of how various states count and record their data.

The date attribution for confirmed cases and performance of multiple tests on the same individual are two more potential sources of bias. Confirmed cases are often recorded on the date on which the positive test result was received, which has lagged by 7 to 21 days from the date the infection actually occurred, 2 to 12 days until symptoms occurred, and 2 to 10 days waiting for results. The substantial heterogeneity emanates from numerous factors, including regional testing availability, time from infection to symptoms, time from symptoms until testing, and time to process the test and return results. Thus, confirmed case counts have limited usefulness for early detection of outbreaks, since any outbreak is already weeks old before it is reflected in these data. Some municipalities record a case on the date the sample was taken, or even the day symptoms reportedly started. This makes the counts a more accurate reflection of the temporal progression of the virus, but makes the most recent 1 to 2 weeks of data incomplete and biased downwards. In addition, some municipalities adjust for individuals with multiple tests and thus report subject-level testing results, while others report each sample, leading to some degree of overcount.

Given the limitations in testing and incidence data, COVID-related hospitalization data is considered a valuable measure to confirm the occurrence of a true viral surge that may threaten to overwhelm a community’s medical capacity. Unfortunately, these data have been less widely available than case or testing data and with more variable quality. The COVID tracking project attempts to assembles hospitalization data, but for some states such data are unavailable, and often important detailed information like number in ICU, on ventilators, or length of hospital stay are not recorded. In late fall 2020, the USA Department of Health and Human Services began publicly releasing its aggregated hospitalization data. While valuable for confirming that a real outbreak has occurred, the lag time in hospitalization data, typically 2 to 4 weeks after infection, limits its usefulness for early detection of an emerging surge of infections.

Mortality data are perhaps the most widely modeled and discussed quantity in the pandemic. Although a valuable measure of societal impact, mortality data have their own problems and inaccuracies. COVID-related death formally requires a positive PCR test and death attribution, so its reporting depends on testing practices and tends to be a severe undercount of the full number of deaths directly caused by the virus. “Presumed COVID-related deaths” are counted by some municipalities in an attempt to capture more deaths for which no test was done but for which circumstances suggested the cause was likely COVID-19; of course this categorization requires a subjective decision.

“Excess deaths” analyses relative to all-cause mortality from previous years can provide a valuable measure of the impact of the virus, although differentiating deaths caused by the virus vs those related to but not directly caused by the virus is often not straightforward. The case fatality rate can be considered a measure of the danger of COVID-19 relative to other viral diseases, or can be used to compare outcomes across countries. This measure, however, is subject to all of the previously mentioned measurement errors, with confirmed cases severely undercounting infections and capturing the most severe infections with greatest risk of death, in addition to differences in testing policies and the subjectivity of death attribution.

Each of these COVID-19 related measurements contains some information about the pandemic but all have their limitations. Statisticians and other data scientists with expertise in integrating and synthesizing information across multiple data types, while accounting for bias and measurement error, play a critical role in proper interpretation of these data; it is important for these professions to be visible and engaged with media and policymakers to ensure that the accruing data are collected, annotated, interpreted, and communicated appropriately. Experience to date shows that quantitative scientists have been regularly sought out by reporters, perhaps to a greater extent than for any other issue in recent times.

### 3 | MORE ON TESTING

Testing for presence of virus and antibody is essential for understanding the extent of transmission and the size of the outbreak. The first diagnostic test for HIV was the ELISA antibody test, which became available less than a year following the identification of the virus. This test was a useful screening tool as the population at risk was well understood by that time—there was no need to consider widespread population screening—but it yielded a relatively high frequency of false positive results, requiring the use of a supplemental test with much higher specificity to confirm positivity.
Unlike the situation for HIV, when it took more than 2 years from the time the disease was recognized to the identification of the virus, the genome of this new coronavirus was identified early in the pandemic, within a few weeks of recognition of this new illness, leading to rapid development of highly specific diagnostic assays based on the detection of viral RNA via PCR.

For HIV, the populations at risk were limited and well identified, as they were defined by specific behavioral and medical practices. SARS-CoV-2 can affect anyone breathing air in the presence of others, so the need for testing is orders of magnitude greater. While early on, SARS-CoV-2 infections were documented largely by the presence of symptoms such as dry cough, fever, and low oxygen levels, as laboratory testing became more readily available people with suggestive symptoms were increasingly able to get tested; a positive test has become the defining basis for establishing and reporting infection. However, the process of testing for and confirming the diagnosis of COVID-19 on a large scale has proven challenging.

The statistical methods for assessing the accuracy of diagnostic assays and test kits are straightforward, once the pathogen and its molecular structure are known; but there are uncertainties about the currently available tests that can complicate the interpretation of results. A positive PCR test for SARS-CoV-2 is virtually certain to mean the person has been infected, although it does not necessarily mean the infection is currently active. A negative test result is more difficult to interpret. Most tests have been conducted on material taken from swabbing the nasal cavity; improper swab or storage techniques can lead to false negative results. In addition, some infected individuals have limited virus concentration in the nasopharyngeal cavity, resulting in a false negative test. Finally, tests done very soon after infection may give false negative results because the virus has not yet replicated to the point where it is detectable.

A big problem with the PCR tests is the delay in returning results, sometimes up to 2 weeks, resulting from the limited number of laboratories that can process them, especially during times of viral surge. Antigen tests that identify the viral antigen associated with infection, also done by swabbing the nasal cavity, yield results much more rapidly than the PCR test but have much lower sensitivity. Some have argued that these tests have high enough sensitivity to detect active infection and might be useful for containment, but as noted previously, the FDA has recently communicated that, in general, antigen tests are less accurate than PCR-based molecular tests. Test accuracy may also depend on the test setting, for example, with tests administered by health care professionals in a clinic expected to be more accurate than self-administered tests taken at home, a fact rarely discussed or taken into account.

To date, most testing for SARS-CoV-2 has been done on individuals with developing symptoms or known exposure to someone positive for the virus. However, widespread testing of populations, followed by quarantine of those who test positive, and tracing and quarantining of their contacts, has long been considered the ideal way to control an infectious disease outbreak. Schools and universities are particularly interested in implementing such testing programs. However, adequate supplies of tests have not been available in most areas, and the costs associated with testing millions of people are substantial.

Testing of pooled samples, followed by testing of the individual samples only when the test of the pool is positive, can be used for screening donated blood for HIV and Hepatitis C and has been proposed for community testing programs for SARS-CoV-2. For this to be an effective approach, one needs to know how much dilution from negative samples will still allow the virus to be detected in the pool; this will require reasonable estimates of the sensitivity of individual tests. Statistical methods for implementing and interpreting pooled testing have been available for some time, going back to testing World II draftees for syphilis and has been used in both human and veterinary settings. Both the FDA and the Centers for Disease Control and Prevention have provided guidance for manufacturers of diagnostic tests who wish to have their tests authorized for pooled testing.

4  |  NATURAL HISTORY

The initial recognition of AIDS as a syndrome was the occurrence of unusual opportunistic infections and malignancies, particularly pneumocystis pneumonia and Kaposi's sarcoma, in homosexual men. It was another 2 years before the causal virus was identified. During this period, understanding of the natural history of AIDS was limited to the interval from the first development of symptoms until death. Once the virus was identified and the amount of virus in the body could be measured, the long latency period from infection to manifestation of symptoms was recognized and documenting the natural history was fairly straightforward—over many months or years, the immune system was gradually
destroyed, leaving the infected individual subject to a variety of infections and malignancies, ultimately leading to death. With less than a year following recognition of SARS-CoV-2, there are many important and as yet unanswered questions about the natural history of COVID-19. Developing information is coming from observational data obtained from hospital records, as well as from clinical trials.60,61

Unlike HIV infection, COVID-19 is an acute infection that often manifests itself with symptoms appearing within days of infection, and with the course of infection typically extending no more than a few weeks. As noted earlier, however, many infected individuals will never become symptomatic, and a small number of so-called “long-haulers” will have extended symptoms, typically inflammatory in nature. Another major difference is that most individuals infected with COVID-19 recover, with virus cleared from their bodies without intervention. Even for those who become ill enough to require hospitalization, the vast majority recover—early estimates were in the neighborhood of 75% to 80%,62,63 with more recent data showing substantially lower mortality rates,64,65 likely due to increasing numbers of younger individuals becoming infected as well as improved approaches to patient management. The primary means of disease progression is respiratory, with a large proportion of hospitalized patients requiring supplemental oxygen66 and some ultimately requiring ventilators.67 Particularly problematic is the development in some patients of an inflammatory response, or “cytokine storm,” that has led to organ damage in some patients, and is implicated in many of the severe complications and deaths from this disease. Other serious sequelae include excessive clotting, kidney damage, and neurological effects.68,69 In children, rare cases of a multisystem inflammatory syndrome similar to Kawasaki disease have been observed, in some cases days or weeks after recovery from COVID-19.70 There is increasing concern about cardiovascular effects, with cases of inflammatory heart damage reported in previously healthy people, some of whom had only mild cases of COVID-19.71 The frequency of such sequelae or the risk factors for their development are yet to be determined; additionally, the possibility of long-term consequences of infection that may not appear for some time after recovery from infection cannot be ruled out due to the limited time the infection has been with us. Long-term observation of individuals who recover from an infection will be needed to identify any such sequelae.

Many other aspects of the natural history of COVID-19 remain to be studied. The lack of widespread community testing with follow-up of anyone found to be infected limits our current ability to describe the natural history from the time of infection, including the very important estimation of the proportion of those infected who will remain asymptomatic or minimally symptomatic—those in whom the disease never becomes manifest or causes such minor symptoms that the affected person is not motivated to seek testing. Estimates have been made from the experience on the Diamond Princess Cruise ship72 and on the U.S. Navy ship USS Theodore Roosevelt,73 but it is not clear how representative these populations are with respect to the course of the infection. As noted earlier, different studies have produced a wide range of estimates of the ratio of asymptomatic to symptomatic cases. One meta-analysis74 found that a high proportion of transmission is likely from asymptomatic and presymptomatic individuals, and another study demonstrated that unlike other coronaviruses such as SARS-CoV-1 and MERS, much of the infectious viral shedding for SARS-CoV-2 occurs in the first week of infection, before symptoms are evident.75 The abundance of spread from asymptomatic and pre-symptomatic individuals is one of the defining characteristics of SARS-CoV-2 and contributes to the challenges of containing this pandemic.76

Some estimates of time from infection to emergence of symptoms have been made on the basis of case series in which identifiable exposures provided reasonable estimates of time of infection and for whom there was follow-up for emergence of symptoms using new methods for developing such estimates with limited data.77,78 Understanding the upper limit of the incubation period is important in order to set an evidence-based period of quarantine for anyone known to have been exposed to an infected individual. Currently, this period is set at 10 to 14 days, but this could change if information emerges that suggests the incubation time may be longer for some proportion of those infected.

Even more importantly, we do not know the extent to which infection itself, whether or not it ever becomes symptomatic, will result in immunity from future infections—and if so, what the duration of that immunity would be. Recent reports of individuals who have had a second infection several months after recovering from an initial infection have been documented to be from a different virus strain from the first infection, raising concerns that the duration of postinfection immunity may be quite limited for some.79 It is not clear how many or which individuals are susceptible to such rapid re-infection, although the prevalence of infection during the pandemic would suggest that millions of re-infections would have been observed by now if duration of immunity was limited to a few months; reported cases of re-infections, however, are limited to anecdotes in the dozens or hundreds. Much more follow-up will be needed to derive reasonable estimates of the duration of immunity following recovery from infection.
There is a growing but incomplete knowledge of the immune response to SARS-CoV-2. Unlike HIV, which rarely induces neutralizing antibodies capable of controlling the infection, many of those infected with SARS-CoV-2 generate a vigorous immune response with almost all infected individuals demonstrating a strong neutralizing antibody response that is more likely to be effective with magnitude depending on disease severity. The relationship between antibody levels and susceptibility to reinfection requires more study as with B-cell memory, neutralizing antibodies can be quickly produced with future exposure even after the original antibody levels wane. Another relevant aspect of the immune response is the production of T-cells, which can recognize and destroy viral cells without antibodies. T-cell response has been observed in most individuals exposed to SARS-CoV-2, and even in some individuals not exposed to the virus possibly from exposure to other coronaviruses. This T-cell response may not be sufficient to confer immunity to infection, but may partially explain why some infected individuals quickly recover with no or only mild symptoms. Further characterization of the mechanism and durability of immune response is crucial to the construction of effective treatment and prevention strategies, including vaccines.

5 | IDENTIFYING RISK FACTORS AND PROGNOSTIC FACTORS

There are two aspects to assessing risks related to COVID-19: risk factors for becoming infected, and prognosis for disease progression and mortality among those infected. For HIV, it became clear fairly quickly that the infection was blood-borne. Exposure to blood from an infected person, whether via sexual intercourse (through tearing of tissues), blood transfusion or via travel through the birth canal, was the primary predictor of infection. Thus, behavioral issues primarily defined prognosis for becoming infected—anal sex with an infected partner, use of condoms, number of sexual partners, needle sharing. Medical factors affecting prognosis included transfusions of blood or blood products, and for infants, an HIV-infected mother.

For COVID-19, the factors known to be associated with becoming infected are also behavioral/occupational, driven by its primary mode of spread through airborne aerosol or respiratory droplets: exposure to large numbers of individuals in close quarters, especially in enclosed areas, and use or nonuse of masks. No demographic or clinical characteristics have been identified that predispose people to becoming infected that are not explained by behavioral/occupational/environmental factors that result in higher exposure.

The prognostic factors so far identified are those that are readily identified as patients present for treatment and are routinely recorded in the medical record. Factors already identified include demographic characteristics such as age and race, and presence of co-morbidities such as heart disease, pulmonary disease and diabetes, and obesity. Clearly there is much overlap among these factors; more needs to be done to determine which are most important, whether level of severity of these comorbidities matters, and whether the medications taken for these comorbidities play any role in prognosis.

Currently, there is much interest in going beyond these factors to investigate biomarkers and genetic factors that might predict the course of acute disease, the propensity for some of the less common manifestations such as extensive clotting, the potential for long-term sequela, and, very importantly, response to treatment and vaccines. In children, identifying factors that may increase risk of developing the rare Kawasaki-like syndrome will be important.

There has been much speculation about the lower susceptibility of children to infection, given that relatively few symptomatic cases in children have been observed, relative to other age groups; this could be due to children being more likely to remain asymptomatic rather than any resistance to infection. The susceptibility of children to infection, and the degree to which infected but asymptomatic children can transmit the disease to others, is a major unknown that is hindering adequately informed decisions about school operations.

6 | EVALUATION OF TREATMENTS AND VACCINES

Once AIDS was defined as a clear syndrome, physicians treating AIDS patients tried a variety of approaches to treatment that had some biological plausibility, and some randomized trials were conducted. As potential treatments were considered, statisticians studied the relationship of the disease course to various biomarkers, hoping to find early outcomes that could predict disease progression and mortality and that could be valid therapeutic targets—the “surrogate endpoint” problem. A systematic drug discovery approach was taken by the drug company
Burroughs Wellcome. In 1984, the drug azidothymidine, originally developed as a cancer treatment, was among many agents tested by the company for possible in vitro activity against HIV. When results appeared promising, the NIH began phase 1 testing, which rapidly progressed to a randomized placebo-controlled trial after the phase 1 results showed remarkable improvement in patients’ health status.96 The drug, commonly known as AZT, clearly improved mortality in the randomized trial97 and was approved by the FDA in 1987, 6 years after the disease was first identified. Treatments that were able to keep the virus from replicating indefinitely did not become available until 1995.98

The initial search for therapeutics to treat COVID-19 has been similar to that for HIV—early scattershot approaches to try treatments with some biological plausibility in small, often single-center studies, while some researchers in academia and industry, with better tools than were available 40 years ago, are meticulously combing their way through existing compounds, hoping to find drugs whose known mechanisms suggest that they might be active against SARS-CoV-2.99

Because COVID-19 is an acute illness, and the time from infection to appearance of symptoms is within a few weeks (rather than the years for HIV), researchers are moving much more quickly to identify effective treatments. Over a period of only a few months, some randomized trials showed benefits63,100 and lack of effect101,102 for several treatments; trials of others are underway.

In contrast to traditional vaccine development programs, numerous vaccine candidates were quickly formulated and their development and study have proceeded at an unprecedented pace. Trials of vaccine candidates began in the summer of 2020; several trials have already demonstrated short-term positive efficacy and safety results.103-106 The high rate of viral transmission in the fall of 2020 that has continued into the winter of 2020/2021 has led to rapid accrual into the large, randomized phase 3 studies for the most advanced candidates, with five large trials already completed and demonstrating efficacy ranging between 70% and 95% and strong safety profiles; phase 3 trials for several other candidates are on target to yield definitive results by early to mid-2021. Four vaccines have already received EUA from regulatory agencies in the U.S. and/or Europe and deployment began in December 2020 in front-line workers and vulnerable populations, with tiered expansion plans to the rest of the population being laid out for 2021 pending sufficient production and distribution. Two of the currently deployed candidates utilize a new mRNA-based strategy that requires special handling and storage that raises logistical challenges, raising hopes that some of the other vaccine candidates that are less expensive and easier to handle will be authorized in the first or second quarter of 2021 in order to help accomplish the international deployment that may be the key to bringing the pandemic to a close and transition SARS-CoV-2 to an endemic virus that is manageable and less severe.

7 | CONCLUSION

Before COVID-19, the last extremely large global infectious disease outbreak—one that we have not yet overcome—was HIV/AIDS, which was first recognized 40 years ago. We have not yet learned how to cure HIV infection, nor do we have a vaccine (despite having tested multiple vaccine candidates in large-scale efficacy trials),107 but we did quickly understand that behavioral interventions such as condom use and avoidance of needle sharing were extremely effective in preventing transmission. Later on, medical interventions that were effective in minimizing risk of transmission treatment of mothers during pregnancy to prevent mother-to-child transmission, preexposure prophylaxis with antiviral drugs) were identified,108-110 and approaches to limiting community spread have been studied.111,112 With COVID-19, we currently have only a very limited therapeutic armamentarium; however, the reports of highly effective vaccines in late 2020 offers substantial hope for bringing the pandemic under control. In the meantime, effective behavioral measures such as mask-wearing, physical distancing, and use of hand sanitizers have been encouraged but gaining universal adherence to these measures has been challenging. Given a large number of therapeutic and additional vaccine candidates already under study, the exceptional efficacy and safety profiles seen for the approved vaccines, and the short-term nature of the latency period and the disease itself, we have reason to hope that we will soon be able to bring the pandemic to an end and reduce COVID-19 to a medically manageable disease.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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