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Artificial Intelligence and Machine Learning for HIV Prevention: Emerging Approaches to Ending the Epidemic

Julia L. Marcus[1] · Whitney C. Sewell[1] · Laura B. Balzer[2] · Douglas S. Krakower[3]

Abstract

Purpose of Review We review applications of artificial intelligence (AI), including machine learning (ML), in the field of HIV prevention.

Recent Findings ML approaches have been used to identify potential candidates for preexposure prophylaxis (PrEP) in healthcare settings in the USA and Denmark and in a population-based research setting in Eastern Africa. Although still in the proof-of-concept stage, other applications include ML with smartphone-collected and social media data to promote real-time HIV risk reduction, virtual reality tools to facilitate HIV serodisclosure, and chatbots for HIV education. ML has also been used for causal inference in HIV prevention studies.

Summary ML has strong potential to improve delivery of PrEP, with this approach moving from development to implementation. Development and evaluation of AI and ML strategies for HIV prevention may benefit from an implementation science approach, including qualitative assessments with end users, and should be developed and evaluated with attention to equity.

Keywords Human immunodeficiency virus (HIV) · Prevention · Machine learning · Artificial intelligence · Data science · Big data

Introduction

Artificial intelligence (AI) is ubiquitous in our everyday lives. Online retailers suggest products tailored to our shopping history, music services learn from our listening habits to recommend songs we might like to hear, and navigation apps suggest the fastest route based on traffic patterns. Other applications of AI, such as widespread use of self-driving cars, are on the horizon. Just as AI has made our daily tasks more efficient, it has the potential to improve clinical care, including HIV care, by optimizing disease diagnosis, treatment selection, and risk stratification for prevention strategies [1, 2]. Essentially, AI is the use of computers to perform tasks that normally require human intelligence. Whereas early AI systems relied on decision rules and extensive programming, improvements in data collection, statistical methodology, and computing power have driven the increasing popularity of machine learning. By accounting for complex interactions, machine learning can identify unanticipated patterns in large datasets and make predictions accordingly [3].

With nearly 40,000 people contracting HIV each year in the USA [4] and 1.7 million new cases globally in 2018 [5], novel strategies are urgently needed to prevent new HIV infections. In early 2019, the US government launched the Ending the HIV Epidemic initiative, which aims to reduce HIV incidence in the USA by 90% by 2030 [6]. The primary goals of this federal initiative, as well as global efforts, are to expand access to antiretroviral therapy for persons with HIV and preexposure prophylaxis (PrEP) for those at high risk of HIV acquisition.

Laura B. Balzer and Douglas S. Krakower contributed equally to this work.

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✉ Julia L. Marcus
julia_marcus@harvardpilgrim.org

Whitney C. Sewell
whitney_sewell@harvardpilgrim.org

Laura B. Balzer
lbalzer@umass.edu

Douglas S. Krakower
dkrakowe@bidmc.harvard.edu

[1] Harvard Medical School and Harvard Pilgrim Health Care Institute, 401 Park Dr, Ste 401, Boston, MA 02215, USA

[2] University of Massachusetts Amherst, 715 North Pleasant St, Amherst, MA 01003, USA

[3] Beth Israel Deaconess Medical Center, Division of Infectious Diseases, 110 Francis St., W/LMOB Suite GB, Boston, MA 02215, USA

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Thus, the extent to which AI approaches will be useful for HIV prevention will depend on their ability to catalyze scale-up of antiretroviral therapy and PrEP in the communities that are most likely to benefit.

The purpose of this review is to identify applications of AI, including machine learning, in the field of HIV prevention. We also discuss patient and provider perspectives on AI for HIV prevention, potential challenges related to bias and equity, and paths forward for implementation research.

What Are AI and Machine Learning?

As with most things related to "big data" and "data science," debates ensue as to the exact definition of AI and its relation to machine learning [7•, 8]. For the purposes of this review, we broadly define AI as the ability of machines to process and respond to environmental input with human-like intelligence. Likewise, we broadly define machine learning as the process by which computational and statistical algorithms "learn" from data, usually with limited human input.

Machine learning algorithms vary in their complexity. For example, traditional regression models are, in fact, basic machine learning algorithms; given a dataset as input and an objective, these algorithms learn coefficients to satisfy a modeling goal (e.g., maximizing the likelihood). In contrast, artificial neural networks are more complicated approaches that were designed to mimic information flow and learning in the human brain. Ensemble or stacking methods are particularly promising because they improve upon any given method by combining several algorithms together [9, 10]. Super Learner, for example, uses sample splitting (i.e., cross-validation) to build the best weighted combination of predictions for a set of candidate algorithms [11, 12]. Machine learning algorithms also vary in their application. We focus our discussion primarily on the use of machine learning to improve prediction while also noting its role in other aspects of HIV prevention.

Machine Learning to Identify Potential PrEP Candidates

In 2019, the US Preventive Services Task Force issued a grade A recommendation for the use of PrEP in people at risk for HIV acquisition, noting the need for improved tools to identify potential PrEP candidates [13, 14]. Multiple HIV risk scores have been derived, primarily for MSM; several are available online, including the San Diego Early Test Score and Sex Pro [15, 16]. Many of the applications of AI for HIV prevention have built on this work by using machine learning to identify people who might benefit from HIV testing, PrEP, or other risk reduction strategies (Table 1).

Healthcare Settings

Electronic health records (EHRs) are ubiquitous and contain rich information that can be used to predict HIV risk, including demographic characteristics, social history, diagnoses, laboratory tests and results, and prescriptions. Several recent studies have developed and validated HIV risk prediction algorithms that use EHR data and machine learning algorithms to identify patients who are at increased risk of HIV acquisition and may benefit from discussing PrEP with a provider [17].

With data from Atrius Health, a multispecialty group practice in MA, Krakower et al. evaluated over 40 machine learning algorithms and more than 100 EHR variables to predict which patients would contract HIV [18••]. A standard metric for prediction models is the area under the receiver-operator characteristic curve (AUC), also known as the C-statistic, which represents the probability that a randomly drawn case (i.e., person who acquired HIV) from the study population will have a higher risk score than a randomly drawn non-case [19]. LASSO, a type of penalized regression, was the best-performing algorithm with a cross-validated AUC of 0.86, a substantial improvement compared with previously developed HIV risk prediction tools. The study team externally validated their machine learning risk score in a Boston community health center specializing in care for sexual and gender minorities and found that predictive performance may be moderately lower when transferring algorithms to independent clinical settings, possibly because of differences in HIV epidemiology, patterns of health care utilization, or EHR use. Future work should explore tradeoffs between universal algorithms, which may be disseminable across healthcare settings but with reduced predictive performance, and algorithms tailored to each healthcare setting, which require greater investment of resources but are likely to be highly predictive in their specific patient population.

In a parallel study, Marcus et al. developed and validated an EHR-based prediction tool using the LASSO approach to identify potential candidates for PrEP among 3.7 million members of Kaiser Permanente Northern California [20••]. The final algorithm had 44 EHR predictor variables, including male sex, living in a ZIP code with high HIV incidence, urine positivity for methadone, and number of positive tests for urethral gonorrhea in the previous 2 years, with a cross-validated AUC of 0.84. To understand the added value of including data elements from multiple EHR data domains, the authors compared their final algorithm to strategies based only on variables related to sexual orientation and sexually transmitted infections (STIs), finding that the algorithm including additional data domains had a higher AUC and sensitivity but lower positive predictive value.

Finally, Ahlstrom et al. leveraged nationwide electronic registry data in Denmark to identify patients likely to benefit from HIV testing or PrEP, evaluating multiple sets of

Table 1 Applications of artificial intelligence and machine learning for HIV prevention

	Region	Setting	Population	Data source	Key studies
Machine learning to identify people who might benefit from HIV testing, PrEP, or other risk reduction strategies	USA	Healthcare	General population	Electronic health records	Marcus et al. [20••], Krakower et al. [18••], Feller et al. [22•]
	Denmark	Healthcare	General population	Nationwide electronic registry data	Ahlstrom et al. [21]
	Eastern Africa	Population-based intervention study	General population	Community-level randomized trial	Balzer et al. [24••]
	USA	Smartphones	MSM	Ecological momentary assessments	Wray et al. [28]
	USA	Social media	General population	Twitter	Young et al. [29]
Virtual reality tool to promote HIV serostatus disclosure	USA	Online and healthcare	Young MSM living with HIV	Qualitative interviews	Muessig et al. [30]
Chatbots to deliver HIV prevention information	USA	Social media	General population	Medical and public health resources	Brixey et al. [33]

PrEP preexposure prophylaxis, *MSM* men who have sex with men

predictors and multiple machine learning algorithms [21]. Ridge regression, another type of penalized regression, was the best-performing algorithm with a cross-validated AUC of 0.88. When calibrating their prediction algorithms to a sensitivity of 90%, they estimated that 384 people would have to receive an HIV test to identify one undiagnosed person with HIV. Given the low positive predictive value of algorithms with an outcome as rare as incident HIV diagnosis, future research should evaluate the cost-effectiveness of applying these algorithms to detect undiagnosed HIV infections or identify PrEP candidates in clinical care settings.

In all three of those studies, only data from structured fields were used to predict HIV risk. In contrast, Feller et al. used machine learning algorithms to predict incident HIV diagnoses in an academic medical center in New York City, finding that natural language processing of data from clinical notes (i.e., free text) improved predictive performance [22•]. This is an intuitive finding in that clinicians might document HIV risk behaviors that are not routinely captured by structured fields, such as sexual behaviors or HIV status of sexual partners. Natural language processing is a potential strategy for optimizing future EHR-based tools to identify patients who might benefit from PrEP, although the benefits to predictive performance will need to be balanced against the additional computational resources required.

Population-Based Research Setting in Eastern Africa

Machine learning has also been used to identify potential PrEP candidates in the generalized epidemic setting of rural Kenya and Uganda. As part of the ongoing SEARCH study (NCT01864603) [23], potential candidates for enhanced PrEP counseling were identified through an inclusive approach based on serodifferent partnerships, a machine learning risk score [35], and self-identification of risk [68••, 69]. In a separate modeling study, Balzer et al. used data prior to PrEP rollout to compare the efficiency and effectiveness of various algorithms to predict HIV acquisition within 1 year [24••]. Population-based data on HIV serostatus and demographic predictors (but not sexual behavior or STIs) were collected at multi-disease health fairs with home-based follow-up for non-participants [25]. Using these data, the researchers compared the performance of three approaches: (1) a risk group approach, for which they created an HIV risk score by summing the number of known risk groups to which each person belonged; (2) a model-based approach that used standard regression methods to create an HIV risk score from model coefficients; and (3) the machine learning approach Super Learner, which combined together predictions from LASSO, generalized additive models, stepwise regression, and main terms regression [11].

The cross-validated AUC for the machine learning approach was similar to previously developed HIV risk scores in Eastern and Southern Africa [26] but only slightly higher than for the model-based approach (0.73 vs. 0.70). However, the AUC provides limited information about how a classifier will perform if implemented, especially with a rare outcome such as HIV [27]. When Balzer et al. evaluated measures of efficiency that incorporated sensitivity, they found substantial advantages with machine learning. For example, to correctly classify a fixed 50% of new HIV cases as high risk (i.e., 50% sensitivity), the machine learning approach would need to identify only 18% of the population as candidates for PrEP, compared with 27% for the model-based strategy and 42% for the risk group strategy. Likewise, when Balzer et al. evaluated the sensitivity achieved when limiting the rate of positive predictions (i.e., the number identified for enhanced prevention services), they found substantial advantages with machine learning.

As HIV risk prediction tools continue to be developed and optimized, efficiency and effectiveness metrics, such as those used by Balzer et al., can help evaluate predictive performance and guide future implementation. The selection of metrics may depend on the programmatic priorities and resources specific to each setting. For example, Zheng et al. developed a modified Super Learner to handle realistic resource constraints in a generalized epidemic setting; its goal was to minimize the total number of PrEP candidates, subject to a minimum sensitivity [35]. In low-prevalence healthcare settings in the USA, risk cutoffs may be tailored to the number of patients per provider that is feasible and acceptable to flag for PrEP discussions during primary care visits. In all settings, machine learning should be used to enhance identification of persons at higher risk of HIV acquisition, but should not be used to screen out individuals from PrEP eligibility.

Smartphones and Social Media

Smartphones and social media offer unique opportunities to engage people in real time, potentially including interventions to promote condom or PrEP use when sex is anticipated. Wray et al. used a smartphone application to collect ecological momentary assessment data on daily sexual intentions, arousal, and behaviors from MSM who were not on PrEP [28]. The authors used machine learning methods to predict condomless anal sex, finding that data collected throughout a given day can be used to identify 74% of condomless anal sex events before they occur. They posit that these real-time data could potentially be used to guide "just-in-time" interventions (e.g., text messages) through smartphones to promote HIV risk-reduction behaviors, such as condom use, but note that their algorithm would miss one out of four condomless anal sex events and trigger unnecessary intervention too frequently. Social media offer an additional opportunity for collection of real-time HIV-related data, although the opportunities for intervention in this setting are less clear. Using a dataset from Twitter, Young et al. applied machine learning to predict tweets defined by a content expert as being related to HIV risk behaviors [29], suggesting that social media data could augment traditional epidemiologic surveillance by identifying HIV risk behaviors in real time. Although these studies are a proof of concept, the feasibility and impact of AI for HIV prevention in this context are as yet unknown.

Other Applications of AI for HIV Prevention: Virtual Reality and Chatbots

In addition to machine learning for prediction, AI has also been used to facilitate HIV serodisclosure. In a small pilot study by Muessig et al., investigators developed and evaluated the Tough Talks virtual reality program to help young MSM roleplay HIV serostatus disclosure, with the goal of increasing protective behaviors against HIV transmission [30]. The authors gathered qualitative data through focus groups with young MSM living with HIV on their HIV serodisclosure experiences, which were then used to create a database of utterances that commonly occur in discussions about HIV serostatus. Participants could pick a virtual character (i.e., an avatar) and roleplay various disclosure scenarios with the virtual reality program, with most finding the tool acceptable but some finding it unnecessarily complex and cumbersome to use. A randomized trial is planned to test the effect of this AI tool, delivered online versus in a clinic setting, on HIV viral load and condomless anal sex among young MSM [31].

Chatbots, also referred to as conversation agents, have been a relatively limited application of AI for HIV prevention to date. Chatbots can anonymously engage with users through voice or text messaging, using machine learning to prepare an appropriate prompt or response based on previous interactions. Chatbots have gained momentum alongside rapid developments in natural language processing, social media, and mobile applications [32]. In 2016, Brixey et al. implemented a chatbot for sexual health information on HIV/AIDS (SHIHbot) on Facebook Messenger, providing users with information from a response database compiled from professional medical and public health resources [33]. In 2018, the US Department of Health and Human Services piloted a chatbot on Facebook Messenger during the International AIDS Conference, learning the importance of tailored, conversational, and multimedia content for future chatbot development for HIV prevention [34]. In addition to delivering HIV-related information, chatbots could potentially support people in decisions related to PrEP use or adhering to PrEP or antiretroviral therapy, but these applications have not yet been explored.

Role of Expert Knowledge in Machine Learning for Prediction

There is often a notion that expert knowledge and machine learning are incompatible. However, in the above examples, machine learning was a promising tool for identifying PrEP candidates because it was informed by human knowledge. For example, when using EHR data, Krakower et al. and Marcus et al. first reduced the sets of candidate predictors from thousands of potential variables to 134 and 81, respectively, that were suggestive of HIV risk. Likewise, Balzer et al. created new predictors based on known epidemiology, such as being a woman aged 15–24 years, and Young et al.'s demonstration of the potential for social media data to improve HIV prevention was only possible after a human's expert classification of the outcome (i.e., tweet related to HIV or not).

Another key role of humans is telling the machine our goal. Although the default may be to improve the accuracy of predictions, we can also tailor the objective function to better align with our programmatic goals, as discussed above. Ultimately, the most sophisticated AI tool cannot escape the age-old adage of "garbage in, garbage out,", so human input, vision, and oversight remain essential.

AI and Machine Learning for Causal Inference

Embedded in each of the above examples is a causal inference problem: we want to know the causal effect of such AI-based interventions on health outcomes. Causal inference is distinct from machine learning and other AI tasks in that we are not simply predicting or observing. Instead, we are asking about how the world would change if the underlying conditions changed [8, 36, 37]. For example, we do not only want to know how well virtual reality simulates disclosure among young MSM. We also want to know how the rates of condomless anal sex would differ if all young MSM used the virtual reality program versus if the same individuals, over the same time period with everything else kept the same, did not use the program.

When inferring the effect of HIV prevention strategies, machine learning has traditionally taken the form of regression modeling to characterize the relationships between the exposure, outcome, and confounding variables (i.e., common causes of exposure and outcome). Modern advances in machine learning algorithms, however, provide several opportunities to improve our estimates of causal effects [38–40]. For example, machine learning was recently used to increase precision and thereby statistical power when estimating the impact of a universal HIV test-and-treat strategy on a variety of outcomes in three cluster randomized trials [23, 41, 42]. In observational settings, machine learning has reduced bias from regression model misspecification and allowed for more flexible control of measured confounders [43]. Finally, in both observational and trial settings, machine learning has reduced bias from incomplete ascertainment of HIV status and HIV RNA levels when assessing population-level HIV viral suppression [44].

Patient and Provider Perspectives

The ultimate impact of AI on health outcomes in HIV – what matters most to people – will depend on whether, when, and how patients and healthcare providers adopt these strategies into their lives and practices. However, few studies have assessed patients' and providers' perspectives on AI applications in HIV prevention. In one qualitative study, US primary care providers welcomed the use of machine learning algorithms to identify potential candidates for PrEP based on their EHR profiles. Providers believed that these tools might decrease missed opportunities to offer PrEP and normalize conversations with their patients about HIV risk. However, providers also expressed hypothetical concerns about machine learning, including the potential for breaches of patient privacy and skepticism about using algorithms with "black box" prediction methods that providers could not easily comprehend [45]. In a qualitative study with sexually active MSM, participants expressed mixed opinions on whether they would trust clinical prediction rules to accurately estimate an individual's risk for HIV acquisition [46], so they would likely have similar concerns about machine learning approaches. These studies suggest a need to present machine learning interventions to end users in ways that engender trust in these tools, including their security and results, because opaque and non-intuitive predictions are likely to remain unused.

Although not specific to the use of chatbots for HIV prevention, in a survey of 100 practicing physicians in the USA, respondents indicated both positive and negative opinions about the use of chatbots in healthcare more generally. They believed that these tools could offer administrative benefits, such as automated scheduling of patient appointments, but believed that they could not provide detailed diagnosis and treatment information and might even pose risks if they increased patients' inappropriate self-diagnosis [47]. A mixed-method assessment of patients' views on chatbots in healthcare found similar ambivalence, with most patients indicating receptivity to these tools but also concerns about their accuracy, cybersecurity, and ability to empathize [48].

The concerns raised by patients and providers on the use of AI in healthcare are similar to those that have been raised about applications of AI outside of healthcare settings. For example, concerns about self-driving cars include their ability to be less error prone than humans (i.e., accuracy), potential threats to cybersecurity, and unintended consequences related to equity (e.g., job displacement). Like AI applications outside of health, AI for HIV prevention is most likely to be successful if it is developed and implemented in collaboration with stakeholders and with attention to users' diverse potential concerns.

Bias and Equity Considerations

There is mounting evidence that AI, including machine learning algorithms for risk prediction, can be inadvertently biased, with the potential to perpetuate health disparities [49–53]. By design, machine learning algorithms learn from historically collected data, which were generated in the context of interpersonal and structural biases. Given disparities in the HIV epidemic and PrEP uptake [54–56], it is imperative that machine learning approaches to HIV prevention are developed, implemented, and evaluated with careful attention to fairness. First, investigators must increase their own awareness of the biases that shaped their data, including structural racism, misogyny, and discrimination against sexual and gender minorities [57]. Second, investigators must work to ensure that machine learning tools result in equal benefit, performance, and resource allocation across priority groups [57]. Rajkomar et al. offer strategies for promoting fairness at each stage of the algorithm development and implementation process, including engagement of diverse stakeholders, measurement of algorithm performance across groups, and monitoring of patient outcomes throughout deployment [51•].

Existing HIV risk prediction tools based on Centers for Disease Control and Prevention criteria for PrEP use, specifically recent sexual behaviors and STIs, have been shown to underestimate HIV risk among Black men who have sex with men [58, 59]. For this reason, Marcus et al. assessed algorithm performance by race in the Kaiser Permanente study. Their final algorithm had equal ability to predict HIV acquisition among Black and white patients, while most of the approaches based on only variables related to sexual orientation and STIs had lower sensitivity for Black compared with white patients. These traditional HIV risk factors may be less prevalent in the EHRs of Black individuals because of medical mistrust [60], poor communication between patients and providers [61], or structural racism in the healthcare system [62]. Incorporating additional data elements that rely less on patient or provider behavior, such as location of residence, may reduce racial bias in HIV risk prediction tools. Using the final algorithm, 28% of patients with high HIV risk scores were Black, compared with only 4% of PrEP users, suggesting that EHR-based algorithms could prompt sexual health discussions with Black patients who might not otherwise be identified by themselves or their providers as potential PrEP candidates.

Marcus et al. also evaluated predictive performance by sex, finding that none of their algorithms were able to predict HIV acquisition among women, whose HIV risk might be largely dependent on the unmeasured risk factors of their partners. Given small numbers of transgender women and the relatively low HIV incidence and difficulty of identifying HIV risk factors among cisgender women, it might remain challenging to develop HIV risk prediction tools for women in the USA. Using EHR data from public health clinics in Florida, an ongoing project seeks to address this gap by developing and validating an algorithm to identify women who might benefit from PrEP in a county with elevated HIV incidence among women [63]. Several HIV risk scores have been developed specifically for women in sub-Saharan Africa [26, 64]. Balzer et al. found that machine learning improved the efficiency and effectiveness of HIV risk classification, as compared with risk group and model-based approaches, among both men and women as well as younger (i.e., aged 15–24) and older adults.

Implementation and Future Research

AI can catalyze major changes in healthcare delivery if it is implemented successfully and to its full potential. For example, machine learning algorithms can diagnose diseases based on imaging with similar accuracy as providers [65] and are being used in routine care, raising theoretical concerns that AI might eventually replace radiologists [66]. Yet, most machine learning algorithms have had limited impact because they are not deployed broadly in care settings [3, 67]. Thus, it will be important for developers of AI for HIV prevention to consider and plan for future implementation at all stages of development to optimize acceptability, feasibility, and impact.

In the SEARCH study, machine learning with data collected on tablets was used as part of a strategy to help identify candidates for PrEP in real time during community-wide HIV testing in rural Kenya and Uganda [68••]. Among 69,121 HIV-negative persons screened, 12,935 were identified for enhanced PrEP counseling: 10% via serodifferent partnerships, 54% via machine learning risk score [35], and 36% via self-identification as being at risk of HIV acquisition [69]. In the USA, several new studies will examine whether EHR-based machine learning algorithms can be used to identify PrEP candidates and improve prescribing in diverse primary care clinics. Additional research will use machine learning to integrate data from social media, behavioral surveys, and HIV prevalence databases to deliver tailored HIV-prevention information to MSM on social media. Further studies will use machine learning to process phylogenetic and geospatial data to identify HIV hotspots.

Because these projects use sensitive personal data to generate targeted strategies for HIV prevention, they have the potential to stoke fears of “Big Brother” surveillance among patients and providers. Thus, collaborative research approaches that seek meaningful input from stakeholders will be important to facilitate successful implementation, sustainability, and population impact on HIV transmission.

Conclusions

Persistently high rates of HIV incidence worldwide, as well as inequities in HIV incidence and uptake of PrEP, indicate a need for innovative strategies to improve implementation of HIV prevention. Machine learning algorithms have strong potential to optimize delivery of PrEP by improving identification of people at high risk of HIV acquisition. Programs can use these algorithms to catalyze conversations about PrEP as part of an inclusive approach to PrEP, and this approach has moved from development to implementation. Through virtual reality programs and chatbots, AI could also be used to improve HIV serodisclosure or automate the delivery of HIV-related information, with the potential to support people in decisions related to PrEP use or adherence to PrEP or antiretroviral therapy. Human expertise and input are essential throughout AI development and implementation, including qualitative assessments with end users to maximize feasibility, acceptability, and impact on HIV prevention. Finally, given disparities in the HIV epidemic and PrEP uptake, AI and machine learning approaches must be developed and evaluated with attention to bias. With equitable and effective development and implementation, AI and machine learning strategies could have a meaningful impact on the HIV epidemic.

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Human and Animal Rights and Informed Consent All reported studies with human subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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