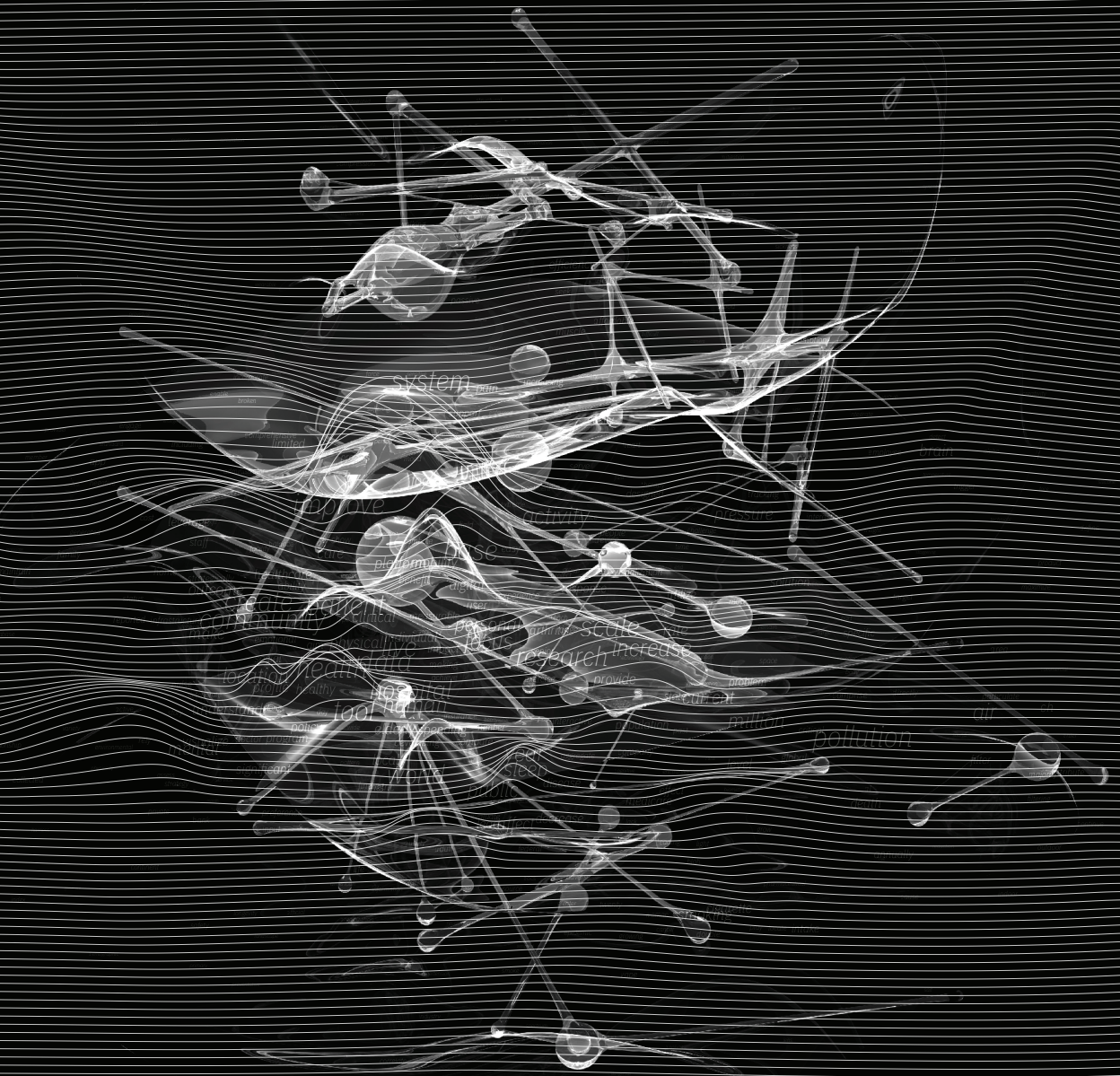
mde Master in Design Engineering at Harvard

HEALTH SYSTEMS



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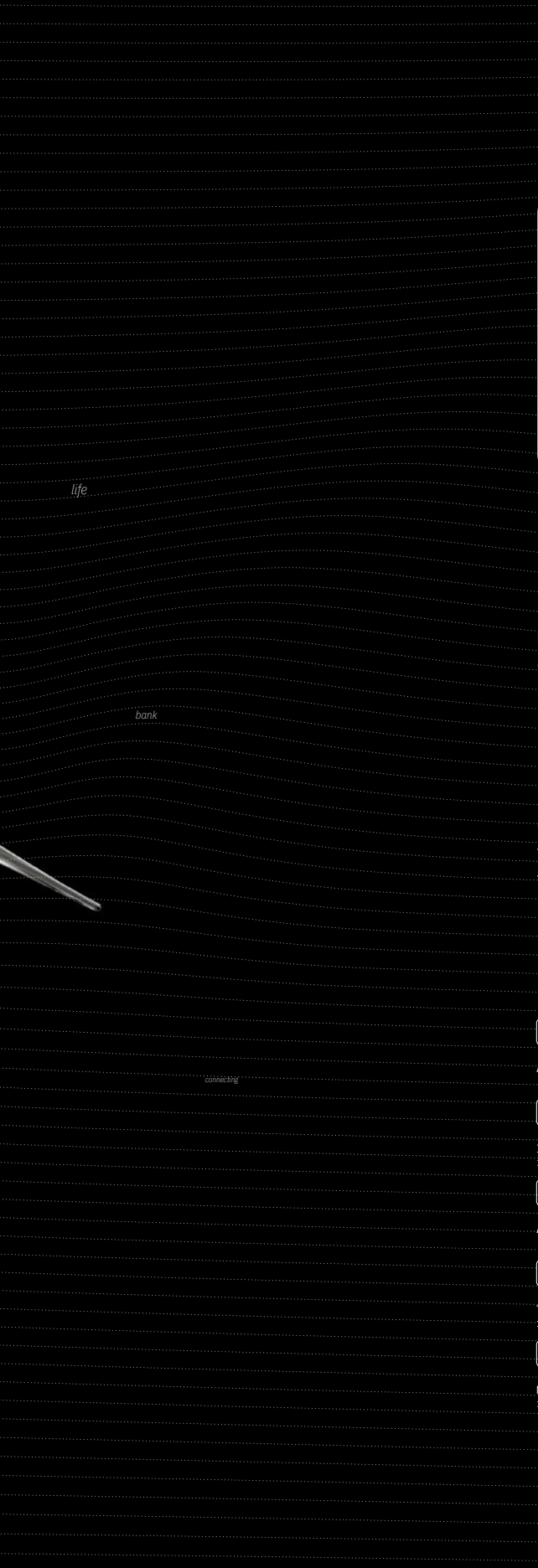

P

PATIENT

How do I receive care? With the abundant data and resources available to inform decisions on our well-being, navigating the health system has become a burdensome task. These projects survey broad data and construct comprehensive pathways to better health outcomes to aid in answering the question: how and where should I, a patient, receive care?

P1 AFIA

Affordable, fast, intuitive, accurate STI viral testing

P2 CODA

Individualized therapy space designed to address mental health in the 21st century

P3 OLIVE

A moisture detecting smart-belt for ostomy care

P4 PAIR

The perfect pair of air shoes to correct gait and pressure for a better stride

P5 PHARMA 2100

Mapping funding allocations of the global healthcare system to investigate the balance between preventative and chronic care

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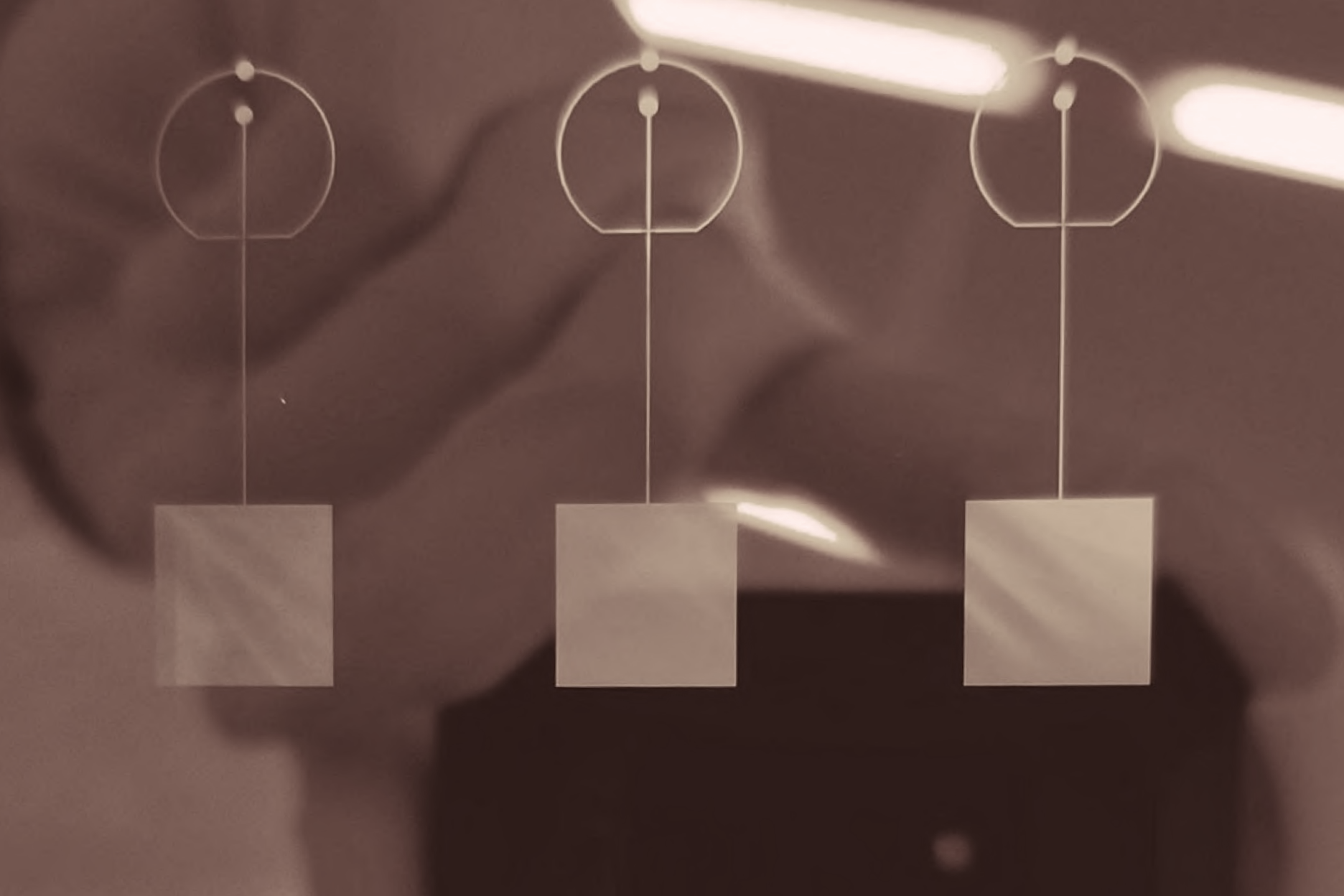
AFIA

Affordable, fast, intuitive, accurate viral STI testing

37 million people in the world have HIV, and this number continues to grow. Diagnostic attrition is a major cause for concern in many parts of the world, a situation in which patients enter the diagnostic pipeline, but drop out of their testing schedule prior to receiving a final diagnosis. AFIA addresses this problem by reducing detection time for HIV infections via a field-deployable, low cost, standalone kit. Currently, patients who are interested in being formally tested and who are unaware of their condition do not take the steps necessary to get tested or treated (if necessary). Even though testing is not to blame for the epidemic, it does play a significant role in awareness, transmission, and patient agency. How can we increase patients' awareness of their condition and reduce attrition in a field of complex biological, medical, and regulatory constraints?

Julian Siegelmann, Kenneth So, Janet Sung, and Kiran Wattamwar



ABSTRACT

37 million people in the world have HIV, and number grows at the rate of millions per year. Attrition remains a problem where patients enter the diagnostic pipeline, only to drop out of their testing schedule before reaching a final diagnosis. The team aims to reduce attrition rates by reducing detection time for HIV infections. Due to a complex and strenuous diagnostic pipeline, many patients who are initially interested in a formal diagnosis lack timely feedback to inform steps toward treatment. Even though testing is not to blame for the epidemic, it does play a significant role in awareness, transmission, and agency. Current HIV testing may lack sensitivity to cost, is slow, and requires training, relegating it to expensive procedures often performed in labs. The need for sensitive testing is furthered by the "U=U" movement (undetectable = untransmittable), which was recently backed by the CDC. Given our market, regulatory challenges, and technical requirements, a good solution is (1) simple and intuitive, (2) fast, (3) deployable and easy to use in the field, and (4) affordable.

The team created a flow cytometry-based assay that implements microfluidic processes to safely, accurately, and quickly count viral load measurements in 1 mL of blood. The microfluidic device is implemented in concert with a companion app and phone accessory, which is designed to fit all standard phone types used in Africa and America. This allows both in-clinic and at-home usage. To circumvent the regulatory need for lab-based testing, the device is designed with simplicity and disposability in mind. The research and solution is presented here on four different scales: (1) the viral scale (technical interactions), (2) the device scale (components), (3) human scale (clinical and user experience), and (4) the systems scale (national rollout).

A PRIMER ON HIV

For HIV patients, there are multiple roadblocks to getting the care they need. Clinics in rural Africa are few and far between, leading to long travel times. Once at the clinic, congestion creates long wait times and patient anxiety, resulting in some parties leaving prior to receiving their test results. Currently, a patient who is interested in taking a test follows a rigid testing pipeline to confirm a positive diagnosis.

First, the patient must find a clinic. This alone can present a large barrier to those who live in rural regions or those who lack adequate access to healthcare funding to cover testing costs. Depending on available resources, clinics may lack the resources to service their patients. Additionally, the need for labs requires batch testing and formally trained clinical practitioners, leading to longer turnaround times.

Healthcare practitioners experience the same problems, but from a different perspective: centralized clinics may alienate patients farthest away from health centers, while also increasing patient load beyond capacity for a single point of access, leading to reduced patient/clinician time and elevated exposure to waiting room diseases. Additionally, costly lab equipment and batch processing mean tests cannot be carried into rural areas.

Furthermore, clinical testing is a densely regulated process that, under the regulatory framework of the Clinical Laboratory Improvement Amendments (CLIA) in the U.S., requires the clinics to hand over collected human biological samples to labs for sensitive medical testing. Clinics may not analyze samples themselves, and the submission of samples to labs introduces a significant amount of latency in communicating results back to patients.

These clinical barriers to HIV diagnostics have contributed to high rates of attrition in HIV screening. In order to speed up the diagnostic process, there needs to be a solution that can be safely performed at the point of care. To this end, an intervention that bypasses CLIA requirements is an essential design requirement.

Methodology

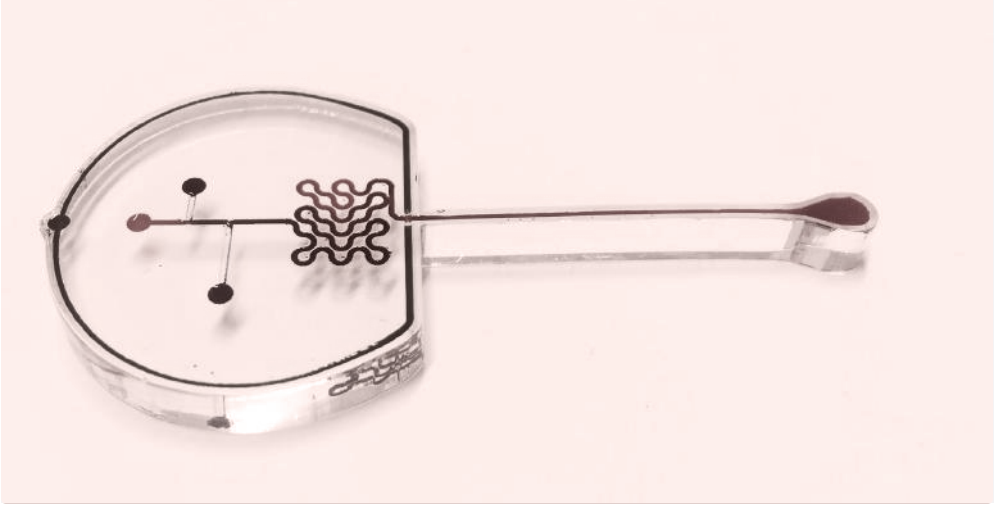
Background

The clinical screening process for HIV is staged and requires an array of sequential tests. Patients without known exposure to HIV will usually take the ELISA (enzyme-linked immunosorbent assay) rapid test first. The ELISA test checks to see if antibodies are present in samples collected from cheek swabs. The ELISA is cost-effective, non-invasive, and fast, but lacks enough sensitivity to determine a positive diagnosis. Patients with negative results drop out of the screening loop at this stage, and others continue with the more sensitive Western Blot test, followed by a Nucleic Acid Test (NAT). These tests are progressively more expensive and require incrementally more technical laboratory processes. NATs are the most precise test, with the authority to confirm a positive diagnosis, but they are also the most expensive in the screening process.

Advanced imaging tools and complicated lab procedures provide feasibility challenges that serve as bottlenecks in rural regions and under-supported clinics. Complicated devices with complex preparation processes, like NATs, which traditionally use gel electrophoresis, are difficult to deploy in remote clinics, where pocket-sized devices may be the most successful. Furthermore, devices must be resilient

↓ MICROFLUIDIC DEVICE

Below is an example of the AFIA microfluidic device, a new, proposed HIV test. Here, you can visibly see the effects of the mixer (the wavy portion of the design) that combines the chemicals from the wells, before forming small droplets. In reality, the diameter of these channels is 50um, smaller than a human hair.



against dust and somewhat mobile to optimize for their usage in the field for clinics that travel (especially those that service rural regions).

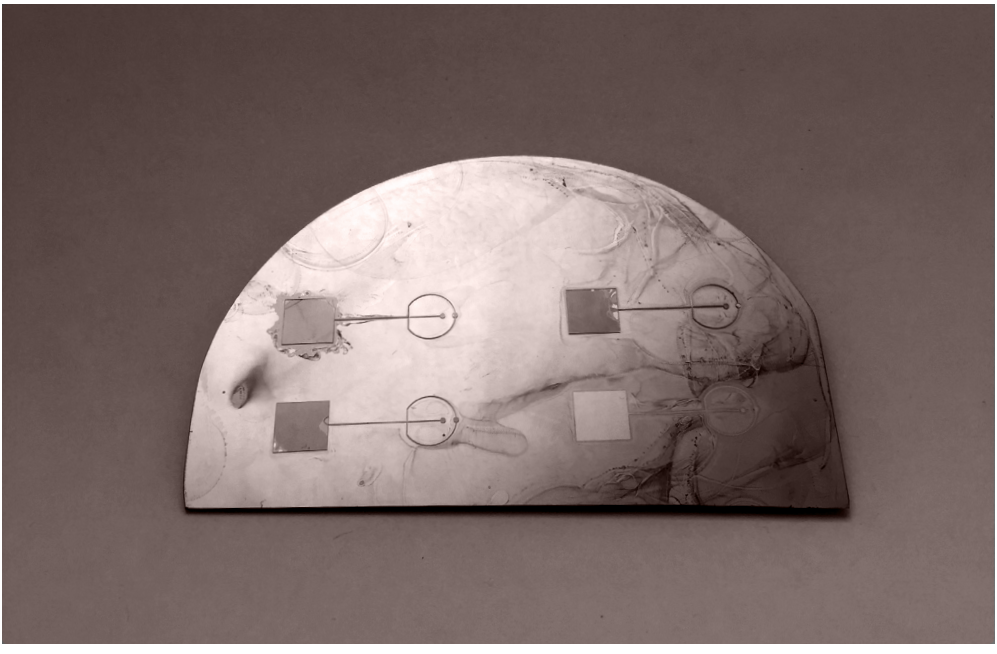
These bottlenecks contribute to a grueling diagnostic process that requires patients endure the psychological burden of waiting, scheduling, and repeated planning. For clinics, regulations require the transfer of samples to labs for testing, creating a time crunch that compounds with a lack of adequate workers to address growing patient populations.

An optimal test given these challenges would be (1) affordable, (2) fast, (3) intuitive, and (4) accurate – AFIA. Affordable tests make individual testing rather than batch testing possible, which can incentivize point-of-care testing. Fast tests reduce the psychological burden on patients who must sit alone, anxiously waiting for results. Intuitive tests make on-site testing possible, instead of requiring labs to intervene. And finally, accurate tests can eliminate the battery of testing and offer a diagnosis from a single test.

In Arabic, “afia” means “good health.” This project, AFIA, embodies the above design principles as a framework for both evaluating the current HIV screening system and as a proposed clinical solution that could reduce attrition in patient diagnostics for HIV.

A New Testing Paradigm

While there are several intervention points in the system that could improve patient awareness of their HIV status, this project specifically focuses on HIV diagnostics. The diagnostics process itself is also broad, spanning improvements in patient experience to reductions in stigma, which can increase the volume of people who get tested. The team decided to address the shortfalls in the device utilized in testing for HIV. While improving the patient experience directly could ease the psychological burden of the process, we saw that addressing the problem at its root – a thorny series of tests – might offer a much larger scale solution for deployment in an array of clinics worldwide.



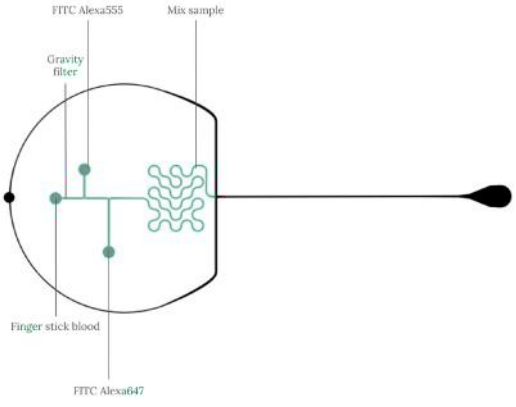
↑ AFIA, AT MICROSCALE

This plate serves as a template for testing the microfluidic design of AFIA's channels, bumpy mixers, and droplet former. The darker sections on the plate above have widths of 50um (smaller than a human hair). By pouring PDMS (a gel-like substance) above these raised sections, letting it set, and removing it, we form small channels and wells in the surface that are used as the base of our device. In that regard, this mask is a "negative" of the Afia device.

The team was also motivated by CDC's research with U=U (Undetectable = Untransmittable), demonstrating that HIV+ people with viral loads below 200 copies / mL cannot transmit HIV to someone else during exposure. While considering how to empower those managing HIV on a daily basis to understand their condition and transmissibility, the team also wanted to explore solutions that could measure viral load in the home. AFIA imagines a future where viral load testing can be performed the same way a diabetic might manage their sugar consumption by using a glucometer, which eliminated venous blood draws as a means of collecting blood samples.

Solution

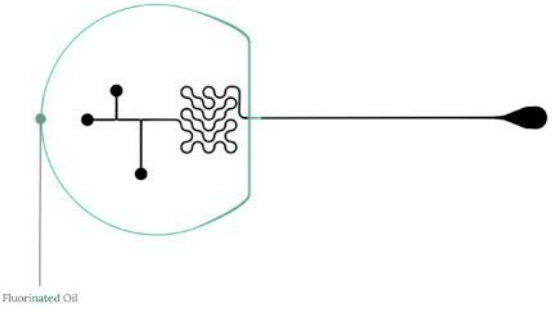
Most existing HIV screening procedures do not meet the standards of affordable, fast, intuitive, and accurate. The team decided to take on the task of counting individual viruses, using a technique from droplet microfluidics. This technique can isolate single viruses and count them through fluorescent markers that attach onto the virus itself. The full solution is mapped in the schematic on the right, along with the corresponding components of the microfluidic device.



← STEP 1: COLLECT A SAMPLE

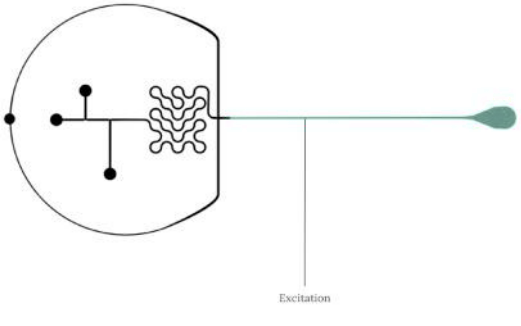
First, samples are collected using fingersticks, which plug into the microfluidic device. Plasma is extracted to reduce noise and prevent markers from binding to other parts of the blood sample. Along with this filtering, a pair of FRET markers that attach to HIV is introduced. FRET pairs fluoresce when they are close to each other. The team uses Alexa555 and Alexa647 antibody dyes conjugated to two nearby antibodies on HIV's surface to illuminate HIV (and only HIV).

The wavy pattern in the schematic is a mixer used to marry the chemicals in each well (circles) together.



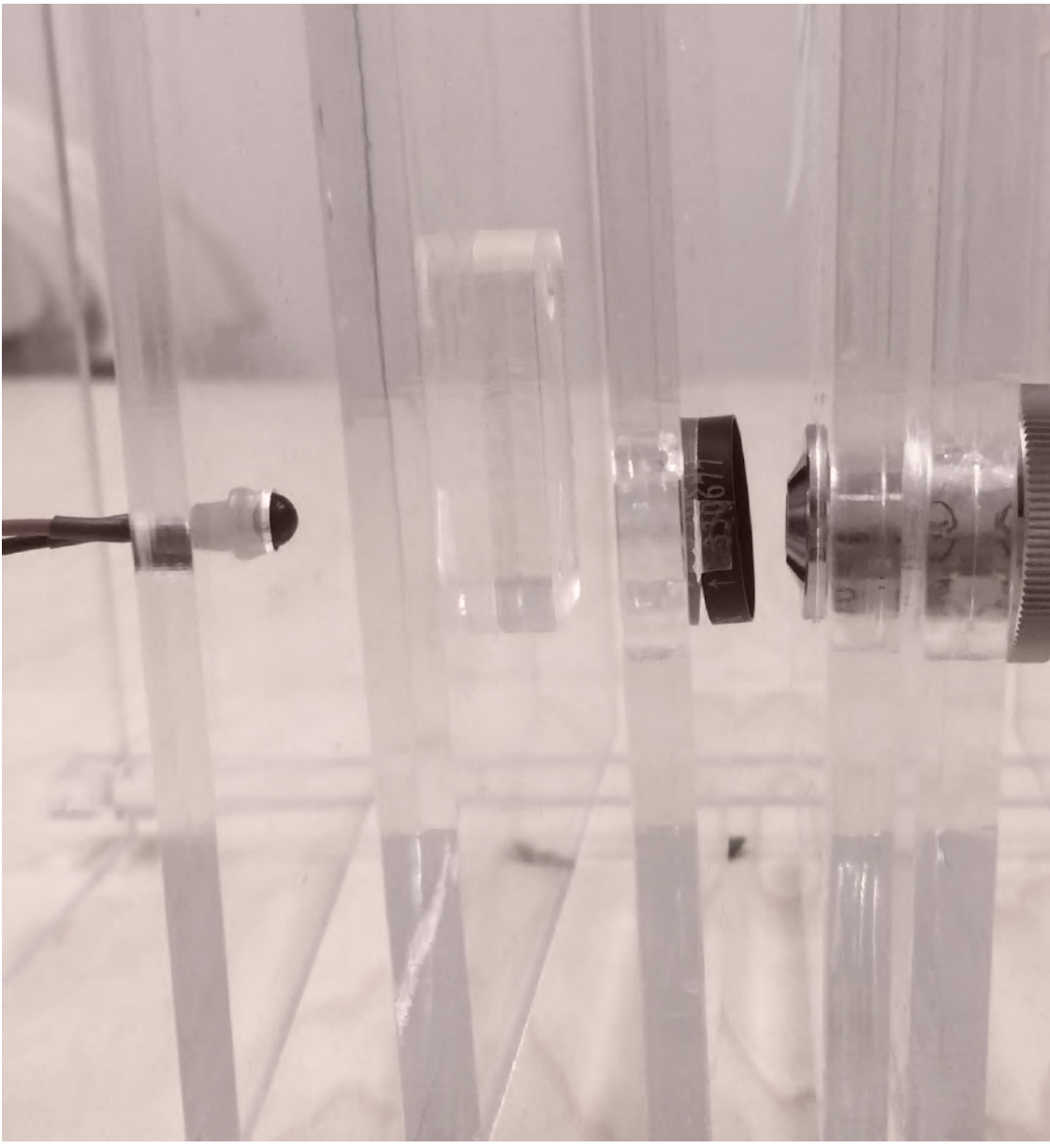
← STEP 2: ISOLATE THE VIRUS

To count the virus' load, the viruses are separated into a single file line so that they can be imaged. This is done by flowing the mixture into a droplet generator geometry, a very small opening where a water-based and oil-based emulsion meet. By varying the flow rates of each, the team is able to generate bubbles of the water-based sample at a desired droplet size of 50um. The fluorinated oil functions as a spacer to keep the bubbles, or vesicles, separated. This droplet size is statistically likely to either have 0 or 1 copies of the HIV virus in it.



← STEP 3: DETECT + QUANTIFY

Using the excitation wavelengths and emission filters of the FRET pair, it is possible to excite each vesicle that passes a specially selected light. If the vesicle fluoresces, it contains a FRET pair and thus, contains a virus. The total count of fluorescent vesicles is a proxy for the viral load. To make this low cost and easy to deploy in the field, the design is an assembly that attaches to a cell phone, which then captures video of the droplets for processing.



↑ LIGHTS, CAMERA, ACTION

This assembly represents the optical array. A light specifically makes FRET pairs visible, lenses focus on the viral scale, and filters specifically isolate fluorscent signals. The full assembly can allow a phone or microscope to see vesicles that contain viruses, and in turn, count the viral load of a sample.

Process

One of the biggest challenges in biology is the reproducibility of experiments. Given the variability in microfluidic implementations, the team thought through many of the nitty-gritty details to make the proposed solution both practical and feasible.

Using fluorescent markers, AFIA aims to capture fluorescence as a signal to mark that a virus is present. Organizing the signal emitted from markers is just as important as the ability to quantify it. An optical system with filter and lens is attached to the phone camera to remove environmental noise and amplify the correct fluorescent signal. By guaranteeing that vesicles have maximally one virus, an algorithm can count the binary signal and obtain the virus load of each sample.

Travelling clinics in the field require additional features: adequate lighting, protection from dust and theft, and portability. Because this work will likely not be done in a lab, the device must be be easy to use, and adjusted to phones used in the regions in which AFIA is deployed.

The team explored several methods of prototyping and fabrication. Microfluidic devices are traditionally prepared by introducing engraved channels into some kind of base material. Many different ways to fabricate the device were considered, from laser cutting, to PDMS, to modular components that enable plug and play applications. Because the channels were around 50um, the team settled on PDMS.

Implementation

AFIA will be implemented in three stages: 1) in the clinical environment, to reduce the time needed to obtain results and reduce the number of uncollected results; 2) in the field, to allow mobile clinics and in-the-field healthcare workers to increase the number of HIV diagnoses; and 3) at home, to increase awareness regarding HIV viral load levels and empower patients to monitor their own health and transmission levels.

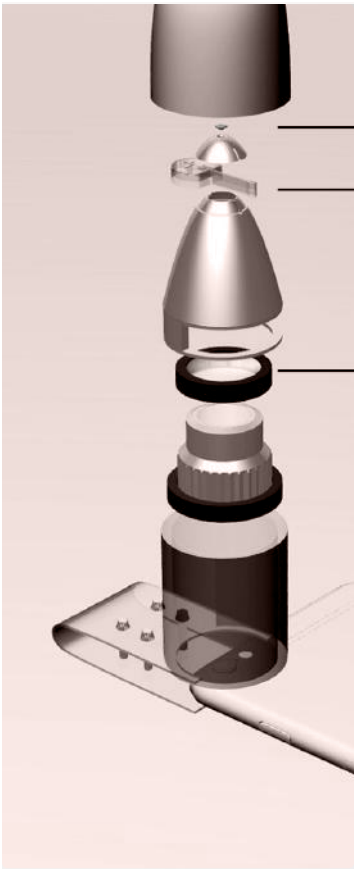
AFIA helps both patients and health practitioners by creating an affordable, fast, intuitive and accurate test that is portable and easily deployable in areas without clinical infrastructure. AFIA improves existing testing on two scales: 1), the physical scale, allowing the test to be deployable anywhere due to its lightweight and disposable nature; 2), in terms of interoperability, as this test can be used by anyone, eradicating the need for clinics and clinicians. This is extremely important, as increased access to HIV testing in rural areas decreases the amount of patients visiting centralized clinics for diagnostic and routine appointments, reduces the spread of diseases in waiting rooms, and reduces the number of patients leaving early due to uncomfortable and long waiting times. We can also roll this out to primary health entities in rural towns, providing accurate testing to even the most remote areas.

By making HIV tests more accessible and increasing the amount of patients that can be seen by doctors, we increase the number of HIV tests taken, reduce the number of uncollected results, and hope to create more transparency and understanding of viral load levels and treatment efficacy. This benefits both the clinic and the patient, both in Africa and the U.S..

We therefore aim to implement our solution within Africa and America first, creating a two-market strategy to monetize one market while subsidizing the other. In order to get our device onto the market, we have to (1) kick-off the medical certification process, (2) test implementation in rural markets, and (3) refine our market strategy to scale appropriately in both the U.S. and Africa.

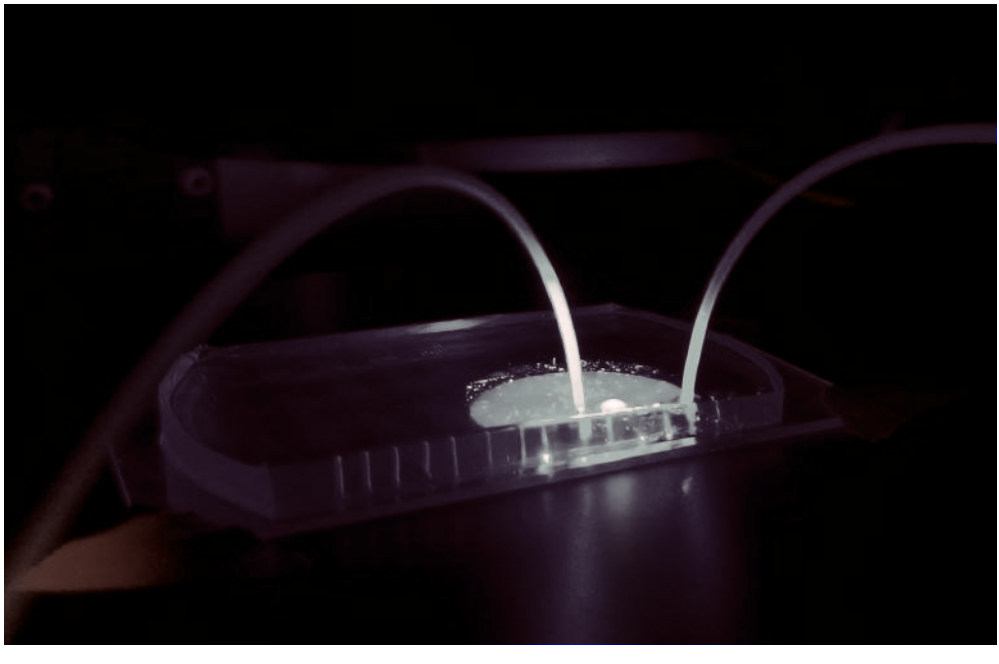
↓ FULL DEVICE

AFIA is not only a microfluidic device, but also a full setup, that can be clipped onto a cell phone camera and covered to protect the imaging from dust when used on the field.



CONCLUSION

In implementing AFIA, we need to understand if we want to pursue public or private partnerships in the African market. Sadly, the NGO landscape can be dispersed and ineffective. A better option might be to work directly with governments. However, how can we ensure that our product does not get hampered by red tape and bureaucratic processes? Additionally, how can we incentivize health entities to implement AFIA? After speaking to experts, we understood that creating private sector profit established an appealing solution to implementation. Most importantly, how can we make testing a rewarding experience for the patient? HIV testing leaves both physical and psychological harm - pricking yourself isn't fun, and being reminded that you have HIV isn't either. There is still substantial work to be done to make HIV consumer testing a viable and desirable experience, but it is clear that advancing this technology development can advance the health and agency of a significant population in spades.



Interviews

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Team Reflections

We were happy to dive deeply into a topic so technical and foreign to us. Our fresh eyes helped us approach and frame the problem with a unique perspective that doesn't often infiltrate this highly specialized space. We are so grateful to the incredible advisors who guided us through our process and the numerous clinicians, nurses, professors, researchers, and labs that offered us a glimpse into the many challenges and important lessons of HIV research.

Getting our hands dirty and really working on fabricating the device and learning additional lab techniques was immensely rewarding. The resources we were given and support to actually fabricate the microfluidic device made our project tangible and real. Early on, we chose to focus our efforts on tackling the technical sides of our project, but realize that this came at the expense of the user experience journey. Nonetheless, we were able to use the insights gained from secondary sources to intuit pain points that our test could solve, and the next step would be to validate that with real users.

We deeply appreciated the opportunity to transcend barriers of academic disciplines and make full use of the resources given to us. By working very closely with studio professors and researchers who made the jump from academia to the private sector, we gained deep insight into how to transition from the lab to the real world. Every interview inspired clarity, learning, and technical expertise that we will carry forward with us as design engineers.