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Biomedical packages

Adjusting drug, bodies, and environment in a phase III
clinical trial

Charlotte Brives

Abstract

Clinical trials are a fundamental stage in a drug's biography for they provide the standard by which a molecule's therapeutic status is determined. Through this process of experimentation, a pharmaceutical substance acquires a new competence – that of treating or preventing disease. This article examines experimentation in drug production, and shows how this complex apparatus not only transforms the status of the molecule but also produces new understandings of and expectations for how people should act. Drawing upon observation of a trial of prophylactic prevention of mother-to-child transmission of HIV, in Ouagadougou, Burkina Faso, I show that the production of this biomedical technology – the therapeutic drug – is coupled with the production of its users. In so doing, I challenge the conception of drugs as bounded objects and instead offer the concept of 'biomedical package', which highlights the social relations that characterise it.

Keywords

medication, technology, objectification, body, experimentation

An ethnography of drugs

In this age of evidence-based medicine, any therapeutic molecule must pass the test of the randomised clinical trial in order to be authorised for commercial sale or to broaden its

clinical use. Such trials provide the basis for assessing the efficacy and potential toxicity of a therapy. The clinical trial – which took on its current form, the randomised controlled trial, in the late 1950s – has attracted considerable interest from social scientists, in particular the rights and treatment of patients, as well as their expectations and demands (Callon and Rabeharisoa 2003; Dalgalarondo 2004; Ecks 2005; Epstein 2001; Nguyen 2010; Pignarre 2007). While scholars have argued that such trials produce a ‘negotiated social order’ (Marks 2000) and highlighted the hybrid character of this ‘gold standard’ of evidence-based medicine (Timmermans and Berg 2003), markedly less attention has been paid to how these trials enact the objects they set out to assess.

Yet this enactment makes the trial a significant stage in the ‘biography of a drug’ (van der Geest, Whyte, and Hardon 1996) for it determines whether the molecule will be given therapeutic status. More specifically, through this experimentation the molecule acquires a new competence – that of treating or preventing disease. While many aspects of drug production and treatments have drawn scholarly attention, how exactly drugs acquire new competences calls for further analysis. Alongside studies that provide insights into the workings of the pharmaceutical industry (Pignarre 2003, 2007), analyse the market terrain of drug development in the United States and India (Rajan 2006) and in Nigeria (Peterson 2014), show how drugs can create or redefine a disease (Greene 2007; Bonetti 2007), and detail how clinical trials recruit their participants (Epstein 2007; Petryna 2009), this article analyses the scientific apparatus that enables the assessment of these drugs and that marks, in this way, a crucial stage in their very existence.

In 2011, I observed a phase III trial that was designed to test and compare the efficacy and safety of two prophylactic drugs for the prevention of mother-to-child transmission of HIV during exclusive breastfeeding (Post-Exposure Prophylaxis or PEP). The trial was simultaneously conducted in Burkina Faso, Uganda, South Africa, and Zambia, and included around 1,500 participants. The two drugs tested, Lopinavir/Ritonavir (a first-generation protease inhibitor, henceforth LPV/r) and lamivudine (a nucleoside analogue reverse transcriptase inhibitor), were at the time of the trial already in use treating HIV infection. The objective of the trial was to broaden the drugs’ competences by testing their capacity in preventing mother-to-child transmission of HIV through breastfeeding.

Breastfeeding is a significant cause of mother-to-child transmission,¹ and HIV-positive mothers are offered two strategies for limiting the risks of postnatal transmission: use formula milk or breastfeed exclusively with early weaning at four months (WHO/UNICEF/UNFPA/UNAIDS, 2007). While formula is widely used by HIV-positive mothers in the global North, it was presented in this trial's protocol as far less accessible or effective for women in sub-Saharan Africa for many reasons. Powdered milk is expensive; water for preparing formula may be contaminated, causing diarrhoea and other infections; and using formula or early weaning can cause family and community members to suspect that one is HIV positive. As one midwife explained to me in an interview, 'If you stop breastfeeding too early on, everyone will know' (17 March 2011). Indeed, sub-Saharan mothers who do not breastfeed are often stigmatised, which is all the more difficult in a context where disclosing one's HIV-positive status is still relatively rare, even between partners, and where fathers continue to occupy a privileged position in all decision making concerning their children (Desclaux and Alfieri 2009; Tijou-Traoré et al. 2009).²

The aim of the experimental design, which enables the mothers to breastfeed up to forty-nine weeks, is both to obtain biological results (are the drugs under study able to limit HIV transmission?) and to positively impact the social and family contexts of the trial participants. If the molecules prove to be effective, the trial protocol states, they would help reduce both the stigmatisation mothers face and the potential health risks linked to using breast milk substitutes. Thus, beyond their prophylactic competence, the drugs also carry a moral and normative dimension in terms of ideas about what being a 'good mother' means in Africa today.

Technical objects and normativity

Scholars have worked to explore the normative dimension of drugs (see, for example Whyte, van der Geest, and Hardon's *Social Lives of Medicines* (2003) and Dumit's *Drugs for Life* (2012)). Akrich's work on 'technical objects' can help flesh out this dimension. In 'The De-description of Technical Objects', Akrich (1992) argues that the technical object has a 'script' that defines relations and produces a 'geography of responsibilities'. During the design process of

¹ The protocol states that at the time of its design it was estimated that each year approximately two hundred thousand children worldwide were newly infected through breastfeeding. Risk of transmission through breastfeeding was estimated to range from 5 to 20 percent, with the risk increasing with the duration of breastfeeding (5–10 percent risk for breastfeeding up to six months; 15–20 percent risk for breastfeeding up to eighteen or twenty-four months).

² However, changes have been observed in the field, with more and more women choosing early weaning in order to be able to work freely (Le Marcis, personal communication).

an object, choices are made that concern both what will be delegated and to what they will be delegated. The technical object, she explains, thus defines ‘actants’³ whose relations shift according to the distribution of competences. This interdefinition of humans and objects ends with the ‘blackboxing’⁴ of the object, which becomes naturalised even as the script can lead to the production of moral judgments.

In her 1996 text, Akrich applies this theory of the technical object to drugs; her ‘brief anthropology of medicines’ is limited, however, to the stage when the drug is put on sale on the chemist’s shelf. This means the entire design stage – in the laboratory and in phase I, II, and III clinical trials (and phase IV even, although the latter usually takes place after the marketing authorisation has been granted) and the commercialisation of the drug (lobbying, marketing, advertising, etc.) – are not examined in her study. In her analysis of women’s health groups investigating the use of new longer-acting contraceptive technologies, Hardon (2006) engages with the notion of ‘script’ and shows how, far from being fixed, it can be reworked and wholly reformulated, bringing new actors into the very process of developing and introducing new technologies. Yet, however productive these concepts of script and technical object might be for understanding drugs and drug experimentation, they remain limited by a conception of drugs as bounded, defined, circumscribed, and delineated objects.

In her study on sex hormone consumption and marketing in Brazil, Emilia Sanabria (2014) shows how ‘the pill’ can be one thing and many, simultaneously. Reflecting on the similarities and differences in marketing and prescription strategies for the pill, she describes how users and prescribers apprehend distinctions between brand-name contraceptives and their copies, and the different modes of administration that are employed. In so doing, she brings into relief the fluid character of the pill and, drawing on Ingold’s work, privileges the term ‘thing’ over ‘object’, a distinction she develops further in later work (Sanabria 2016).

Arguably the clinical trial exemplifies the distinction between object and thing. Although the substances being tested already exist, during the clinical trial they will be evaluated, measured, and standardised, not in isolation but rather in relation to bodies (mothers and their children) and viruses. Building on Whitehead’s philosophy and his reflections on

³ The term ‘actant’ was borrowed from semiology by Michel Callon and Bruno Latour. An actant is defined by its capacity to act, to have an intensity in the course of the action. An actant could be human or nonhuman (objects, organisations, etc.). See Latour 2006 for further details.

⁴ The term ‘black box’, originally used in cybernetics to talk about the representation of a system without examination of its internal operation, was borrowed by Latour (1995) to talk about technical objects or scientific facts considered established. ‘Opening the black box’ signifies going back to the process that led to its development.

chemistry, Barry (2005, 52) argues that ‘molecules should not be viewed as discrete objects, but as constituted in their relations to complex informational and material environments’.

Expanding on the work of Sanabria and Barry, I suggest that a drug’s ‘script’ is nothing other than the crystallisation of specific relations between the molecules, bodies, and pathology studied and measured in the trial. More specifically this crystallisation occurs during phase III, which aims to study the effects, risks, and benefits of taking the medicine, but which goes a great deal further in assigning roles and competences to the various actors involved.⁵ In this way, we might view phase III as the point when substances become medicines, that is to say, when they are turned into ‘types of things that can be distributed, exchanged and disseminated as products’ (Sanabria 2009, 176).

Science and technology studies show how the reproducibility of scientific results depends on the reproducibility of their conditions of production (Latour 1983). The clinical trial, a tool that seeks to study and validate a presumed causal relation, is highly normative: like all experiments, it requires the standardisation of different actors, and it imposes a specific way of apprehending each actor. Indeed, far from merely validating a presumed causal relation, trials construct an apparatus that is able to adjust competences and standardise and control an environment, though only to a certain extent, as we shall see (see Brives 2011, 2013 for further discussion of this apparatus and its limitations).

Through detailed description of the trial procedures, I aim to show how this complex apparatus not only transforms the status of the molecule, but also produces new normativities. All scientific experiments initially involve a standardisation of the various actors involved, and then an adjustment of their behaviours. My analysis describes how the production of this biomedical technology – the therapeutic drug – is intertwined with the adjustment of its users and its environment. At the very heart of the trial is the construction of a match – a process of adequation – between a drug’s potential competences and the competences required of the other actors for its optimal use.

I propose we consider trials as a means to evaluate a specific configuration of relations – in this case, between drugs, bodies, a virus, and environments; this approach makes plain the issue of reproducing trial conditions and the problem of generalisation beyond the trial itself. This framework prompts the question: what exactly does a trial produce? In the discussion I

⁵ Phases I and II, in contrast, are designed to establish the molecule’s physiological role, its administration criteria, and its toxicity; these phases are heavily influenced by the ethical and political choices that govern the very basis of the biological question posed by such trials.

attend to the necessary translations linked to a broadened use of the drugs produced by the trial, and I suggest we apprehend drugs as ‘biomedical packages’ that, rather than being bounded objects, standardise and articulate various actors and shape the environment in which they are included, thereby constituting a powerful tool of governmentality.

Methods

The multisited trial was funded by the French National Agency for Research on AIDS and viral hepatitis (ANRS), and simultaneously took place in Burkina Faso, South Africa, Uganda, and Zambia from 2009 to 2012. This article is based on ethnographic research conducted at the Burkinabe sites of the trial, during the spring and summer of 2011. During that time, I observed and conducted interviews at five locations: the Charles de Gaulle Paediatric Hospital in Ouagadougou, where mothers and their children met with trial staff; the trial’s administrative offices located a kilometre away from the hospital; and three health care centres of the twenty or so responsible for recruiting the mother–child pairs: two in the city and one located in bush country around twenty kilometres from the capital. Every day for the first several weeks, I observed a few dozen mother–child pairs and their formal and informal exchanges with the trial staff, which took place on the hospital grounds, in a building located in a small courtyard near the main building. Once I had obtained their consent, I observed and recorded various medical appointments and conducted several interviews with some of the mothers and with the entire trial team working at the hospital site (which included social workers, doctors, pharmacists, and a nurse). As I did not visit the homes of the mother–child pairs, I did not observe how medicines were stored or administered in the domestic context, though questions related to these practices did arise in both the formal and informal discussions I conducted with the mothers at the hospital.

In parallel, once a week I visited the offices responsible for the trial’s scientific and administrative management and attended staff meetings during which all mother–child pairs visits at the hospital, in other words, both protocol and nonprotocol visits, were discussed and, when applicable, whatever issues had might have arisen (such as recruitment or nurses’ and counsellors’ training). I also went to the three recruitment sites in order to meet the counsellors⁶ in charge of the counselling meetings during which screening and, referral of the HIV-positive future mothers took place.

In addition, in 2012 I took part in the trial’s annual steering committee meeting, held in Montpellier, France. This two-day meeting brought together all the trial’s researchers and

⁶ These counsellors were employed by the medical centres and received extra money from the trial for each mother–child pair they sent to the trial staff for recruitment.

administrators from all four countries. There I observed not only differences in terms of the kinds of issues encountered in each country and the diversity of strategies implemented to respond to them but also the difficulty of comparing data between countries.⁷

The right drug for the job

The drugs tested in the trial have been used widely for the treatment of HIV infection for many years; the trial was meant to assess a potential new use for them, specifically, whether they could be repurposed to limit mother-to-child transmission of HIV during breastfeeding. The trial followed a strict but simple protocol: the child must receive two daily doses of the medication, morning and evening, and must exclusively receive breast milk during the first twenty-four weeks of life (water is excluded, along with all other substances). After this period other foods are gradually introduced into the child's diet. Weaning must occur at the latest in week forty-nine of participation in the trial, with cessation of prophylaxis in week fifty – according to the protocol, this duration was chosen due to the difficulty mothers experience in stopping breastfeeding earlier, even with intensive counselling.⁸

The trial protocol states that LPV/r and lamivudine are just two of the molecules that could have been chosen for testing, and that these candidates were selected on the basis of specific criteria:

1. The drugs have a satisfactory safety profile, especially with HIV-1-negative infants.
2. The drugs have a long half-life.
3. Data is available on the pharmacokinetics of the drug in both newborns and the paediatric population at large.
4. The drugs are available in paediatric formulations.
5. The drugs genotoxicity profile is better than that of AZT.
6. The drugs are not expensive.

Each of these criteria provide insight into the objectives the drugs are meant to meet – they must not present a danger for the paediatric population, there must be solid data available on

⁷ Although these differences are an important and interesting subject of enquiry, I do not explore these issues further here. However, they come to the fore as soon as one considers the generalisation of trial results, including trials concerned with evaluating a process considered by the trial scientists as purely physiological, and therefore universal.

⁸ Again, these decisions are based on a reified conception of the African woman, for an increasing number of women work and choose early weaning in order to continue their occupations.

how the drugs behave in the bodies of newborns (pharmacokinetics), they must be less genotoxic⁹ than AZT (another widely used antiretroviral drug). As they are used to treat children, they must be administered in a suitable form (generally syrup form) and therefore they must have a long half-life to avoid high-frequency administration. Finally, the economic factor is crucial in light of the target population.

The drugs that met these criteria, and that were thus chosen for the trial, were lamivudine and LPV/r. The extensive data available on the safety profile of lamivudine in the paediatric population was considered particularly encouraging. It has a fairly long half-life (five to seven hours), which allows the administration of two daily doses. On the biochemical level, its long intracellular half-life makes it a judicious choice given the working hypothesis of cell–cell interaction in HIV transmission through breast milk. Finally, no serious adverse effects have been reported for the drug.

LPV/r is a well-known pharmaceutical, available in paediatric formulation. Moreover, it is available in developing countries and has proven effectiveness in the treatment of HIV. Its anti-HIV action is stronger than that of lamivudine or nevirapine (which was another potential candidate for the trial), and studies show a relatively low incidence of resistance. The trial protocol explains that LPV/r had not been considered for prophylactic use because there was no available safety data for its use in young children, but it was selected for this study based on ongoing research that suggested positive outcomes in this regard. Thus, the drugs are clearly not chosen at random but according to specific criteria, affording the best match to the consumer's specificities – in this case newborns – based on data derived from pharmacological studies, clinical trials, and observational cohorts.

In Ouagadougou, future mothers are generally recruited as follows: when they attend a prenatal visit in one of the health care centres recruiting for the trial, they are offered an HIV screening test.¹⁰ If the test is positive, and if the mother chooses to exclusively breastfeed her child, she is then referred to the Charles de Gaulle Paediatric Hospital for her first visit (screening 1). There, she meets with one of the trial's social workers who explains the trial's objective and methods and checks whether the mother meets the eligibility criteria. Future mothers must be eighteen years of age or older and at least twenty-eight weeks pregnant, and

⁹ A molecule is said to be genotoxic when it risks compromising the physical or functional integrity of the genome.

¹⁰ This depends on health care centres' correct adherence to national strategies and practice guidelines. Generally, the centres recruiting for the trial employ an 'opt-out' strategy. For more information on the running of these centres and the impact of their participation in a clinical trial, see Le Marcis and Rouamba 2013.

they must agree to follow the national protocol for Prevention of Mother-To-Child Transmission (PMTCT), plan to exclusively breastfeed their baby, and intend to live in Ouagadougou for the duration of the trial. Immediately after this meeting, the mother is taken to the trial doctor, who undertakes a full clinical examination and prescribes blood tests (the samples are then taken by the trial nurse). The candidate must have a CD4 count above 350/mm³.¹¹

If the mother meets all these criteria, she must return to the centre two days after delivery at the latest in order to proceed with a verification of the data and an assessment of the infant's eligibility (screening 2). Infants must be HIV-negative, their physiological and biochemical characteristics must meet certain norms, and they must not exhibit any form of congenital malformation. A simple infection or a minor defect in their biochemical characteristics would render the infant ineligible for the trial.

If the mother–child pair fulfils all these criteria, then after reiterating the trial's objective and methods, and after obtaining the mother's written consent, the pair is enrolled in the trial; this must occur no more than nine days after delivery. Following the mother's visit with the social worker (who assigns an enrolment number that will be used throughout the trial to code all data pertaining to the mother–child pair) and her visit with the doctor (who gathers extensive data concerning the mother's HIV status, her social status, and the PMTCT and HIV prophylaxis since birth), she then visits the pharmacist for the randomisation stage. The pharmacist begins by reminding the mother of the importance of treatment adherence, which had already been discussed in screening 1 and screening 2, and then brings forth a box containing randomisation envelopes, the master list,¹² and an adherence interview form. The pharmacist takes an envelope and opens it, and removes a white card that is inscribed simply with the letter 'A' or 'B'. He writes the woman's name, enrolment number, and enrolment date on the envelope, and then enters the same information onto the master list, adding also the randomisation number inscribed on the envelope and the treatment (A or B) to be taken by the infant.

¹¹ CD4 cells, or CD4 T lymphocytes, are immune system cells, and are the main cellular target of HIV. HIV infection causes a sharp drop in CD4 cell count. Over a certain limit, the body can no longer fight infection. At the time of the trial, the World Health Organization guidelines stipulated that infected individuals should be placed on treatment when the CD4 count dropped below 350/mm³.

¹² This list is highly confidential as it contains the mothers' names, their enrolment number, and their randomisation number. It is thus the only document linking the mother–child pairs and the drug being tested, and consequently only the two trial pharmacists are allowed access to the list.

The pharmacist then takes a bottle containing the medication for the infant. All bottles have a label with a removable strip featuring the batch number and storage date. The pharmacist writes the patient's enrolment number and issue date on the label and on the strip. He then removes the strip and sticks it on the mother-child pair's 'study drug log' form, which ensures the traceability of the medication administered. This enables the pharmacist to quickly identify the relevant bottles and remedy the situation if any kind of problem in the management of the stock is detected after the drugs have been issued.¹³ The pharmacist also writes down the weight of the bottle when the mother returns it on the following visit, in order to measure adherence.¹⁴

Then, he takes a syringe and makes a mark on it with a permanent marker to show the mother the correct quantity to be extracted. He then asks her to administer the first dose to the infant in order to go through the correct procedure with her. LPV/r has an extremely bitter taste, which may make the drug difficult for babies to ingest, and the pharmacist describes what she should do if a problem arises for this or another reason. He explains that she can express a small quantity of milk and dilute the medication in the milk to make it easier for the baby to accept; this solution was implemented once they realised the mothers were having difficulty in getting infants to accept the drug. Finally, he stresses at length the correct storage conditions for the drugs: they must be kept out of reach of other children and kept between 2 and 8° Celsius. Given the generally poor living conditions in Burkina Faso, many families do not own a refrigerator. The pharmacist explains that if the mother does not have a refrigerator, the bottle must be kept in an earthenware cooling pot called a canari¹⁵ and gives the mother money to purchase one. The HIV-positive mother and her HIV-negative infant thus constitute the pair on which the efficacy of the drugs will be tested.

Several additional visits are scheduled: after enrolment (day seven), mothers must return in week two, week four, and week six, and then once a month thereafter. During each visit, the mother-child pair meets successively with the pharmacist (with whom the mother deposits

¹³ The storage conditions of the medication are very closely monitored within the pharmacy; every day the pharmacists are required to write down the actual temperature of the fridge in which the drugs are stored. With frequent power outages, the temperature inside the fridge can rise to as much as 22 degrees Celsius and reduce the efficacy of the drugs. All such data are included in the study.

¹⁴ The study drug log is just as confidential as the master list in that the mother's enrolment number and the name of the medication are recorded on the log. It is therefore never given to the trial coordination centre.

¹⁵ The pot is filled with sand and cool water is poured over it at regular intervals to maintain a relatively low temperature. However, some evidence suggests that the cool sensation the canari gives off is misleading, and the real temperature is not in fact low enough to ensure optimal storage conditions.

the medication bottles from the previous visit), then the social worker, the doctor, and the nurse (if there are any blood samples to be taken), and then goes back to the pharmacist again. The social worker tends to focus on issues tied to the mother–child pair’s family and social context, and inquires about certain issues that are not always easy for the trial doctors to broach, such as the condition of the mother’s breasts, potential problems tied to breastfeeding, difficulties in adhering to the treatment guidelines, or travel plans. But the social workers also offer a lot of advice, including nutritional advice (both for mother and child) and breastfeeding advice (finding the right breastfeeding position, getting the baby to latch, the length of each feeding, etc.). All the information gathered by the social worker is written down on a form she then hands over to the doctor along with the patient’s health card.

The doctor only examines the mother on some of the visits, whereas the child undergoes a full clinical examination on each visit.¹⁶ Each visit follows the same routine: the doctor begins by asking the mother several questions in order to fill out the specific forms for each visit. Invariably, he interviews the mother at length about the child’s diet over the last month, and everything the child has ingested or drunk must be recorded. The very fact that the forms include dietary questions when the protocol stipulates exclusive breastfeeding shows the investigators’ awareness of the kinds of social and cultural realities the mothers and children are negotiating. The mothers are asked about any adverse events the infants might have experienced and, where applicable, the name and dosage of the drugs prescribed. Then the child is examined, measured, and weighed. If necessary, the doctor prescribes additional medication or screening tests. Certain visits include prescheduled tests for the mother and/or child; for these, the doctor fills out a request form and leaves the mother and child with the nurse, who then accompanies them to the laboratory. The mother is informed of the results (viral load, CD4 count, or PCR ARN¹⁷ for the child) during the following visit, unless there is an issue requiring urgent treatment. After the laboratory visit, the nurse takes the mother and child to the pharmacist’s office, which is the final stage of the visit.

The pharmacist checks the contents of the bottles left by the mother on her arrival at the clinic, in order to assess, thanks to a scale linked up to a software programme, the number of

¹⁶ This is the case for both routine visits and for unscheduled visits due to a medical issue.

¹⁷ Polymerase chain reaction (PCR ARN) is a method used for assessing the HIV status of children. This is the most anticipated result for the mothers, and some even return to the health care centre well before their next appointment date in order to get the result, which can entail a long and costly journey.

doses used, and thus calculate the child's presumed treatment adherence.¹⁸ These data are then recorded on a form. The pharmacist proceeds with an adherence interview, which is conducted during each visit, and then issues the medication for the coming month. As the dosage is calculated in relation to the infant's weight, the pharmacist reviews the dosage with the mother: he takes a new syringe, makes a new mark on it, and then asks the mother to administer the morning dose to the infant in order to check that she is conducting the procedure satisfactorily.¹⁹

As this detailed description of the protocol makes plain, in order to test the potential competences of LPV/r and lamiduvine, the trial not only mobilises a number of actors – mothers, infants, doctors, pharmacists, nurses, and social workers – but also specifies material conditions (refrigerator, canari) that are not necessarily established or secure, even for the pharmacists (power outages). But this list is far from complete, as there are many other actors involved in assessing the drug's role who are just as active, but outside the centre: the clinical trial monitors, secretaries, consultant nurses, the biologist, laboratory assistants, principal investigator, promoters, sponsors, statisticians, IT engineers, drivers. Indeed, the trial is not confined within the four walls of the Ouagadougou clinic. While the laboratory in charge of analysing and storing the biological samples is located in close proximity, the data are processed elsewhere, at the coordination centre by a team made up of the clinical trial monitor, a statistician, a data-entry assistant, a secretary, and the scientific coordinator for the Ouagadougou site. The health care centres involved in recruitment for the trial²⁰ must undergo regular monitoring, and the midwives and staff working in these centres must be trained, which entails regular interaction with consultant nurses sent by the trial investigators in an effort to resolve any failures in protocol adherence. The data processed by the coordination centre is then sent off to a city in France to be processed by

¹⁸ It should be noted that the procedure does not assess the frequency of the administration, only the number of doses taken, and it does not take into account any double doses administered when the child regurgitates or expels the liquid.

¹⁹ The whole circuit can take several hours to complete. This depends on the number of mothers with an appointment scheduled, whether or not tests are required, and the number of non-scheduled visits (which can be high, especially during peak malaria season).

²⁰ These were mainly Centres de Santé et de Promotion Sociale (Centres for the Promotion of Health and Social Well-being), but also Centres Médicaux (Medical Centres), which are mostly located in the city, but often on the outskirts, with some located in rural areas. The decision to include sites outside Ouagadougou was due to the great difficulties encountered by the trial investigators in recruiting a sufficient number of mother-child pairs. Consequently, although one of the criteria for enrolment in the trial was residency in Ouagadougou, some of the mothers in fact came from areas situated at a considerable distance from the city (sometimes over forty kilometres from Ouagadougou).

biostatisticians and to be reviewed by the pharmacovigilance committee. The findings of the Ouagadougou trial and those produced in other countries must be scientifically compared. Reports must be sent to the sponsors, who will then analyse the trial's budget statement.

Testing the efficacy and safety of these two molecules in the prevention of HIV transmission during breastfeeding may seem a relatively simple task, but the many steps of this protocol form a rather complex obstacle course.

Standardising interactions

Experimentation requires the objectification of the various entities at stake; in order to generalise the data collected, the entities must be circumscribed and standardised. The standardisation of norms, protocols, molecules, and gestures, and even human beings enables the replication of findings in other sites and with other entities, allowing scientists to make claims about the veracity of the findings (Clarke and Fujimura 1995; Hogle 1995; Keating and Cambrosio 2003; Landecker 2007; Porter 1995; Timmermans and Berg 1997, 2003). The trial effectively redefines the actors, giving them a status that they do not have, or at least not with this specific meaning, outside the parameters of the trial. The eligibility criteria for the mother–child pairs, for example, play a particularly important role, as they indicate which individuals will be capable of producing the data required to analyse the impact of the drugs being tested. The individual selected is the one who best matches or fits the technology under study.

If we keep in mind the initial question posed here – how does a drug acquire new competences – we must then examine further the specific details of the trial, and investigate the trial as an experimental apparatus. What does it look like? How is it set up? How do the researchers go about their tasks?

What the trial's promoters wish to study is the efficacy and safety of two prophylactic treatments in the prevention of mother-to-child HIV transmission through breastfeeding. In other words, LPV/r and lamiduvine must demonstrate their capacity to prevent the virus from passing from one body to the other via a fluid emitted by the first body. Within this framework, the mother's body becomes the source of the virus, or its 'reservoir', to phrase it in epidemiological terms. The mother's body is also the environment in which the virus develops and proliferates, its '*Umwelt*', to use Jacob Von Uexküll's (1965) term, its subjective, perceptual world. The notion of *Umwelt* enables anthropologists to articulate how subjects perceive their surrounding world. Researchers and scientists may see the body in many different ways, but the virus perceives only a few signs in this body. Part of the work of

experimentation in this clinical trial involves redefining the body, rescaling it to fit the virus's *Umwelt*, in order to manage the various interactions in which the virus participates.

In this way, the child's body must be apprehended as a potential living environment for HIV, an environment liable to receive the virus during each feeding. Preventing the virus from entering this environment is impossible within the parameters set by the trial. However, action can be directed onto the potential living environment, by altering it and making it unfit for the development and proliferation of HIV. This is the precise point where the drugs being tested come in, and where their action must be studied. The design under study, presented in its most concise form, is thus as follows: one virus, one of two possible drugs, and two different environments, one with the virus and the other needing to be made unfit to receive it.

The trial eligibility criteria are the standards for the experiment: mothers must be eighteen years of age or older, have a CD4 count above 350/mm³, live in Ouagadougou or its immediate area during the trial, and agree to practice exclusive breastfeeding. Each criterion has an important function. Mothers must live close to the trial so that they can visit the clinic at least once a month for compulsory examinations and treatment refills; this criterion helps to ensure the reliability of the design. Her CD4 count is particularly important because if her count was under 350/mm³, she would automatically be put on a triple antiretroviral regimen.²¹ In such a case, her breast milk would contain some of the antiretrovirals ingested, and the child, also on prophylaxis, would be in danger of overdosing.²²

If we stand back and look at what is actually being monitored among the mothers, mainly their CD4 count and viral load, we find that they are apprehended as the virus's living environment: what is being observed is the virus, via the mother, and what is being controlled are its potential interactions with the child, via breast milk.

The eligibility criteria for the child are far more extensive. In addition to the fact that the child must be HIV-negative at the time of enrolment, certain physiological and biochemical characteristics are tested and monitored. The potential candidate must be free from anomalies: the child's body must be able to clearly demonstrate the effects of the drugs

²¹ These were the WHO guidelines as stated at the time of the trial. These stipulations have since changed. In 2012, a CD4 threshold of 500/mm³ was established for starting HIV treatment.

²² Some mothers in the trial have experienced a sharp drop in CD4 count. In such cases, prophylaxis is stopped, the child continues to be monitored for the remainder of the fifty-week period, and both mother and child are immediately sent back to the health care centre that initially referred them, which must then treat them according to national guidelines.

administered. In other words, any background noise must be removed. The child's body – apprehended as potential environment for the virus – is thus highly standardised, configured even, to enable researchers to read and analyse the interactions between drug and virus in the child's body, but also, crucially, to analyse the potential toxicity of the medication. Indeed, introducing an entity, whatever it may be, into a given environment, necessarily brings about changes. While a drug may render the environment unfit for the development of the virus (efficacy), it must not, however, disrupt the environment too profoundly (toxicity).

Thus summarised, the experimental design set up by the trial seems relatively simple: two environments, one virus, and one of two drugs, arranged in a specific way to measure the drug's efficacy in preventing one environment from being infected by the viruses contained in the fluid from the other environment. However, producing scientific data is no simple affair. A host of studies on scientific research have shown the difficulty of producing phenomena, and of stabilising or replicating them.²³ Studies focused on research in the biological sciences have shown the incredible obstacles scientists face in trying to circumscribe or standardise living entities,²⁴ and even in trying to reach a shared interpretation of what can be observed (Houdart 2007; Brives 2010) – and it is worth noting that these are studies conducted in 'traditional' laboratories. Apprehended as closed, aseptic spaces, laboratories are considered one of the elements in ensuring a certain scientific objectivity, or at least proper control over experimental parameters. Although this conception of the laboratory is somewhat erroneous, or at least highly idealised, the fact remains that strict control over experimental parameters – already extremely complex and never fully achieved in a traditional laboratory setting – is all the more challenging with the kind of unbounded experimentation and open-ended laboratory²⁵ of trials such as this one. Managing the experimental parameters thus takes on an altogether different dimension, stretching far beyond the original confines of the trial.

²³ I would particularly like to draw attention here to a series of laboratory monographs (Knorr-Cetina 1982; Lynch 1985; Latour and Woolgar 1988; Traweek 1988), and Ludwig Fleck's (2005) seminal book. For a historical perspective, see Rheinberger 1997, in particular his definition of experimental designs, as well as Shapin and Schaffer 1993.

²⁴ This is especially the case for studies conducted on model organisms (Clause 1993; Creager 2002; Rader 2004; Kohler 1994; Brives 2011).

²⁵ Marks (2000, 134) offers a fitting synthesis of the clinical trial situation: 'Even the simplest randomised clinical trial is the product of a negotiated social order, replete with decisions – some contested, some not – and with unexamined assumptions'. I seek here to extend this observation to the very construction of the experimental design.

Adjusting behaviours

It is not enough to simply determine strict enrolment criteria for the trial participants and assume they automatically and immediately fit the biotechnology being tested.

Indeed, in my observations it quickly became apparent that the experimental design, although simple in appearance, was in fact extremely demanding, both for the trial staff and the mother–child pairs. This is where each constitutive element of the visits described above takes on its full significance: the social workers constantly discuss the mothers' family and social situation with them, they deliver advice on breastfeeding and nutrition, and they also help ensure secrecy when dealing with mothers who cannot or do not wish to disclose their HIV status; the pharmacists conduct adherence interviews during each visit and check that the mothers have properly understood the entire process; the doctors inquire about any potential health issues experienced by the children between visits, and about any medication that may have been prescribed as a result.

All of these practices may be seen as part of a rather conventional medical and social endeavour, and the well-being of the mother and child are indeed crucial parameters for the therapeutic staff. However, an alternative reading that focuses on standardisation can lead to very different conclusions, yet these in no way contradict the previous perspective. As already discussed, standardisation is a requirement in any scientific experimentation to allow for the replication and generalisation of findings. But in addition to standardising the actors, the use of the drugs being tested must also be standardised. Indeed, the trial assesses the efficacy of the two drugs within strict and fixed usage guidelines. If the bodies need to be standardised in order to read the findings, so must behaviours in order to ensure the findings are meaningful. The trial does not assess molecules – rather, it assesses the interactions between molecules, body, and virus.

The trial requires strict adherence to exclusive breastfeeding in the first six months. Yet this is not always easy, especially in a country in which, traditionally, herbal infusions and purges are part of everyday childcare practices. Mothers must ensure that their child ingests nothing but their milk and the treatment, which is administered twice a day, all in a context where it is unlikely that other family members are aware of their HIV status or of the child's participation in the trial. The challenge of doing so brings into relief the importance of understanding the mother–child pair as inscribed not only within the trial, but also in a domestic space, in other words, of apprehending the pair within a wider network of social

relations.²⁶ As Hejoaka (2009) stresses in a paper on care and HIV secrecy in Burkina Faso, the everyday organisation of the home is disrupted by the imperative to adhere to treatment guidelines and attendant constraints. The mothers often have jobs that are incompatible with the treatment guidelines, and a scarcity of public transport services means their mobility is restricted,²⁷ both of which can negatively impact regular treatment administration and clinic visits.

It is important to note that in addition to these issues, mothers rarely get support from other family members because their HIV status is not generally disclosed.²⁸ Desgrées-Du-Loû and colleagues (2009) found in Ivory Coast that women have difficulty in openly discussing their HIV status with their partners after prenatal screenings, despite evidence of a broad tendency for husbands and partners to be understanding, with very few partners reacting negatively. The same tendency can be observed in Burkina Faso (Makhlouf Obermeyer et al. 2011), including within the trial under study – indeed, one of trial’s social workers described how surprised a participant was by her husband’s caring regard for her when she disclosed her HIV status.

The decision to openly discuss HIV status is dependent on multiple factors, including breastfeeding. As Desgrées-Du-Loû (2011) explains, deciding not to breastfeed in most cases entails disclosing one’s HIV status to one’s partner. The drugs themselves – precisely by enabling exclusive breastfeeding over a six-month period and then mixed feeding up to the forty-ninth week – alter the possibilities for this decision-making process.

In order to assess the drugs’ competences, we must therefore apprehend the mother–child pair in their multiple roles: they are both trial participants and research subjects²⁹ and they are also subjects inscribed in domestic space. The social workers thus deliver extensive

²⁶ Certain studies on breastfeeding deal directly, and in a detailed manner, with such relationships, for it is crucial to take them into account and go beyond the mother–child pair in order to engage with these issues in a relevant fashion (Desclaux and Taverne 2000; Tijou Traoré et al. 2009; Tijou Traoré 2010).

²⁷ The trial covers the mother–child pairs’ transport costs, thus ensuring the regularity of treatment. However, as I discuss further in the conclusion, this is ultimately more problematic than it appears.

²⁸ In addition to the question of secrecy, Hejoaka also notes major changes to the structure of the Burkinese family, observing that the notion of extended family is increasingly under threat. Thus, even in cases where HIV status is known and has been disclosed, mothers may still face significant difficulties in administering treatment to their child.

²⁹ For a detailed analysis of these mother–child pairs as subjects of research, see Brives 2013.

advice to the women on breastfeeding, on finding the right position for the baby and helping the baby to latch, so as to avoid common pathologies tied to breastfeeding such as engorgement, sores, and cracked nipples, which can increase the risk of transmission. They also encourage women to discuss their situation with their partners, and in cases where their HIV status and trial participation has not yet been discussed, the social workers help the women to find strategies for dealing with the situation, and to formulate preplanned answers to the questions they might be asked about their behaviour, their absences, or the baby's strict diet or medication regimen. Indeed the trial protocol provides mothers with cell phones with which they can contact social workers at any time; the social workers' presence both during visits and through mobile communications partly compensates for the lack of family support, which has been shown to be a significant factor in managing the disease (Attané and Ouédraogo 2011). The mothers are thus taught certain gestures (such as particular breastfeeding gestures), to refuse to engage in certain well-established family practices (such as feeding infants herbal teas and bath water), and to resist the intense pressure put on them, most often by their mothers-in-law, to comply with these practices. They also learn how to organise their everyday routine (in order to follow the treatment administration guidelines), and how to manage certain fears (revealing their status).

During their visits with the doctor, they must list everything the child has ingested over the last month, and bring with them any medication the child may have taken for a benign illness. This is explicitly indicated in the trial protocol, which states that mothers are required to keep a diary or log book during their participation in the trial, however, this is impossible to implement due to the very high levels of illiteracy among participants. In fact, I never witnessed a single mother bringing a notebook to the medical visits I observed, not even those who could read and write. Such visits reveal one of the limits of the assessment apparatus: children can fall sick, and resulting treatments mark a point beyond which the researchers can no longer control the experimental parameters. A mother can take an ill child to the clinic to see one of the trial doctors, but financial, family-related, and material factors often mean they have no other choice but to seek help at their usual health care centre. Although the medical staff in these centres are generally aware of the child's participation in the trial,³⁰ the kind of medical care provided is very different, and children

³⁰ The mothers are usually encouraged to participate in the trial by their usual health care centre, and the child's health record does state their trial enrolment number.

may be prescribed numerous drugs, and not always for valid reasons.³¹ When such medication enters the child's body, it disrupts the interactions under study. They must therefore be recorded very precisely in order to be able to analyse their potential repercussions in the future. But in order to achieve this, the mothers must be able to report everything to the doctor, down to the slightest detail.

It is very clear that the design becomes markedly more complex when one takes into account the use (and recording) of other therapeutic drugs in the everyday context. This complexity becomes all the more apparent during the visit with the pharmacist, when he discusses with the mother the difficulties she may have encountered, in particular with adherence or storing medication. Numerous factors must be considered when assessing treatment adherence: the child could regurgitate the treatment, in which case the mother must immediately administer another dose; the medication could be spilled, or administered to other children in the family in the same situation, thus rendering all of the findings invalid; or the medication might be stored in inadequate conditions. A personal or family-related matter might cause the mother to travel and be away from Ouagadougou for over a month and thus be without medication to give to her child for several days.

These examples are far from comprehensive, but they do shed light on a fundamental issue: the mother–child pairs are far from passive recipients of a technology, or biomedical 'guinea pigs', but are active participants in developing this technology and its possibilities for

³¹ While I was working with one of the trial doctors, I observed a visit during which the mother explained to the doctor that she had taken her son on two occasions, just a few days apart, to her nearest care centre. There, two nurses separately gave her a total of ten drugs, including two antimalarial treatments as her child had a fever and various other symptoms. When I discussed this case with the doctor when the visit was over, he gave the following explanation: 'It's a big concern. Because if the mother had come to see me instead, I definitely wouldn't have prescribed all of those treatments. As you are well aware, in the outskirts, people treat symptomatically. If the child vomits, they give an antiemetic, if the child has diarrhoea, then they give something to stop the diarrhoea, if the child coughs, then they give something for the cough, which means that you end up with a lot of medication. But they could have kept it simple, with an etiological treatment, they could have tried to see what was causing all of this, and so reduce the number of different drugs' (interview conducted March 24 2011). What underlies these differences in practice in and outside the trial context is to a large extent the considerable standardisation of the protocols (Timmermans and Berg 2003; Berg 1997). But in the case at hand, what needs to be stressed is the absence of doctors in such care centres, meaning that care and treatment are administered by staff with only limited training.

success.³² The mother–child pairs must learn the trial’s rules and make them part of their everyday lives; and they must alter some of their habits, which may also impact the wider family circle. They do so all in view of assessing the efficacy and safety of two drugs, which may ultimately lead to changes in the everyday practices and habits of a great many others. In this way, day by day the mothers and infants learn to become subjects of research and users of these drugs, a process that is apparent in the behaviours demonstrated during the consultations, for example, in the way mothers spontaneously hand over the medication to the pharmacist without being asked, or go to the nurse to give blood samples, or promptly volunteer information that they know will be significant for their interlocutors. The medication acquires new competences via the new competences acquired by the subjects of research.³³ Bodies, practices, and behaviours must be disciplined and adjusted in order to afford optimal use and the most accurate assessment possible of the competences of the drugs under study.

Conclusion: From ‘drug’ to ‘biomedical package’

The aim of the trial under study here was to extend the therapeutic use of existing drugs to new clinical situations, to give them new competences. While the scientific question is made to appear as relatively straightforward, the present analysis has highlighted the far greater complexity of the actual means implemented and the host of different actors mobilised in order to carry out the endeavour. This only makes the clinical trial all the more interesting, for it necessarily entails a redefinition of its various constitutive entities.

As the trial develops, the pharmaceutical substances do indeed gradually acquire a new status (or alternatively, fail to do so): that of a prophylactic treatment. But this new status, this modification of the substance’s mode of existence, cannot be achieved without other modifications – sometimes superficial, often profound, and invariably never insignificant –

³² I have not addressed ethical questions in the present article. The point raised is therefore not moral, but solely ontological: the mothers and children cannot be apprehended simply as objects of the experimental design due to their high level of investment in the trial (not only in terms of time, pressure, physical and material effort, but also fear and hope).

³³ We could apply the same analysis to the trial staff and doctors: they must learn to interact with the mothers, comply with the experimental procedures, and alter some of their working habits. A similar analysis has already been carried out in a different context, concerning biologists learning to work with single-cell microorganisms, *Saccharomyces cerevisiae* yeasts, a process of becoming experimenters (Brives 2010). We might consider how trial practices ultimately impact the prevention, screening, and care practices of the health care centres involved (see Le Marcis and Rouamba 2013, for an analysis of the effects of trial participation for a health care centre situated outside Ouagadougou).

concerning the status of the other actors involved in the trial: the mothers must learn new practices and will come to acquire specific behaviours. The doctors, while participating in the trial, also practice their profession in a slightly different fashion, in particular regarding the prescriptions they give and the tests they request.³⁴ A mother who does not give her baby water might be perceived as a bad mother by her kin, her co-wives, or her mother-in-law, but will conversely be viewed as a responsible mother in the eyes of the trial researchers. A woman who lies to her partner about her HIV status and the risks for their child may be judged a bad wife or partner by some, and of questionable morality, but from the viewpoint of the trial staff she will be considered a virtuous and brave mother. In this way, beyond their prophylactic effect, the drugs not only produce new normativities but also convey a particular moral code.

The trial does indeed test substances, and ultimately create drugs, but it also tests practices and behaviours that it must ensure will be reproducible – yet it cannot predict their effects in other contexts. Without a good breastfeeding technique and without excellent adherence, the drug might not play its prophylactic role. While it is obvious that taking medication is not reducible to its administration, and that practices take shape in relation to particular social, religious, or economic contexts, it is worth noting that the redirection and redefinition of certain practices, but also changes in the ways of engaging with the body and disease, occur right from the very process of transforming a pharmaceutical substance into a therapeutic drug. While assessment of the molecules entails rescaling the question to make it suitable for scientific investigation, it also requires, in a second stage, a generalisation of the findings. And while generalising the use of a drug can certainly be a fraught process in itself, obtaining, on a large scale, the same findings as those produced by the trial poses a definite challenge for it involves not only distribution of the drugs but also a distribution of the behaviours tied to its use. To bring into relief this redefinition of behaviours and grasp the consequences of the distribution of these technologies, we must closely investigate the scientific and technical aspects of the production of such biomedical technologies, analyse their conformation, and never disconnect individuals as subjects of research from their realities as individuals inscribed in domestic space. No biological efficacy comes without concomitant social, psychological, and cultural changes.

³⁴ With the case under study, it is not possible to observe the impact beyond the trial context as most of the team sought professional opportunities outside of the national health care system once the trial came to a close. The consequences are very different in a context where the trial is integrated into the health care system, as was the case with a trial conducted in Abidjan (see Brives 2015).

Clinical trials test a set of relations between drugs, viruses, and bodies – relations that, although standardised by the trial, largely exceed it, extending to the domestic context, to family and professional relations, to cultural practices, and to the way people relate to the health-care system. In this way, the trial both evaluates and constructs a specific configuration of these relations: it assigns roles and competences to better study and measure them in order to standardise them.

The drug is thus not simply an object, unless one considers it an object at a particular time, in a fixed environment, in which the script can be relatively clearly established, and recognises that self-medication, repackaging, and patient activism can alter the relation between a drug and its use.

This article has argued that we must apprehend molecules in their relations with complex informational, social, and material environments; as Barry (2005, 57) writes, ‘the molecule that is isolated and purified in the laboratory will not have the same properties as it has in the field, the city or the body’. While the drug is defined by its relations with the body, the virus, and the environment at a given time, this analysis emphasises that these are shifting relations that are dependent on the actors’ context, and that generalising the use of the drug entails apprehending it within this network of relations. Barry’s theories on chemistry and his view that it is impossible to establish an identity between the molecule in the laboratory and the same molecule elsewhere, and Latour’s arguments regarding the reproducibility of facts lead me to argue that, at the end of the clinical trial – far from being a fixed, bounded object – the drug is a ‘biomedical package’, a crystallised form of the relations between actors, in which we find the standardised and objectified drug, the disease and the vectors involved, and also a set of requirements that not only concern the populations, both human and non-human, who will be targeted by the drug, but also its environment.

This biomedical package is a grey box that is never totally closed, as its elements can be translated and articulated with a given context, at whatever stage. This leads to two discrete outcomes. First, given the very specificities of the drugs, the nature of their interactions with the bodies and, in the case at hand, with viruses (and the pathologies they can cause, which also fluctuate), the conditions of reproducibility cannot be totally guaranteed. In this way, the very efficacy of a treatment can vary from the clinical trial context to its use in a real context, highlighting the uncertainty that surrounds the implementation of any kind of biomedical intervention. Moreover, considering the drug as a biomedical package rather than an object provides anthropological analyses with a way out of the impasse of positivism when engaging with the fruits of biomedical science, typically exploring usage or context but rarely the actual products of experimental science. Secondly, if we apprehend drugs as a biomedical package that conveys norms and specific conceptions that require not only articulation and translation but also the standardisation of a context, an environment, in order to be

operative, then it constitutes a very powerful tool, namely for governing populations, because implementing the drug concomitantly involves redefining targeted populations and transforming their surrounding environment.

Clinical trials are extremely complex apparatuses that produce temporary assemblages by constraining the actors involved in order to produce what are considered reliable data. And as each trial is constructed according to the question it seeks to answer, it produces a particular, contextual assemblage. What we still need to investigate is to what extent the grey box of the clinical trial might also be apprehended as a biomedical package on a quite different scale.

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