

A Pill for HIV Prevention: Déjà Vu All Over Again?

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Recent FDA approval of tenofovir-emtricitabine for prevention of human immunodeficiency virus (HIV) as a form of pre-exposure prophylaxis (PrEP) has led to concern about implementation of this strategy. Fifty years ago, a very similar national and international debate occurred when the oral contraceptive pill (“the Pill” or “OCP”) was approved. Contentious issues included OCP safety, cost, and the potential impact on sexual behavior—many of the same concerns being voiced currently about PrEP. In this article, we review the social and medical history of OCP, drawing parallels with the current PrEP debate. We also explore the key areas where PrEP differs from its forbear: lower efficacy, presence of drug resistance, and a more circumscribed (and marginalized) target population. A thoughtful approach to PrEP implementation, bearing in mind the historical insights gained from the 1960s, might serve as well as we begin this new chapter in the control of the HIV epidemic.

Keywords. oral contraceptives; pre-exposure prophylaxis; historical insight; birth control; HIV prevention.

On 16 July 2012, the United States Food and Drug Administration (FDA) made history when it approved the first drug shown to prevent human immunodeficiency virus (HIV) in uninfected persons [1]. In this decision’s wake, US providers and public health agencies are faced with the daunting challenge of determining how best to provide pre-exposure prophylaxis (PrEP) to the large population who might benefit while also considering risk and cost [2].

Fifty years ago, experts confronted a similar challenge when the first oral contraceptive pill (“the Pill” or OCP) was approved. The controversy then, as now, revolved around safety, cost, and the potential impact of OCP on sexual behavior. Despite these difficulties, the birth control pill was successfully distributed

worldwide. In this article, we review the social and medical history of OCP and draw parallels with the current PrEP debate (Table 1).

BIRTH CONTROL: BORN OF TWO MOTHERS

The idea for an OCP was born of 2 bold women, Margaret Sanger and Katherine McCormick, both early feminists [3] (Figures 1 and 2). Sanger had a long history of hot-blooded activism for family planning, particularly among the poor. She coined the term “birth control” and founded the organization that became Planned Parenthood. In the 1940s, she became increasingly dissatisfied with available options to prevent pregnancy [4]. Then, at a 1951 dinner party, she met George Pincus, PhD, a leading reproductive endocrinologist, beginning a years-long discussion that led to development of an OCP (Figure 3) [5]. Sanger also found a wealthy, investment-minded partner who shared her vision in McCormick. Together, they approached Pincus in 1953 about the quick development of such a product. Accepting the Sanger-

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Table 1. Oral Contraceptives and PrEP: By the Numbers

Issue	The Pill (Enovid)	Emtricitabine-Tenofovir (Truvada)
Year first on the market (for another indication)	1957 (for infertility)	2004 (for HIV treatment)
Year of FDA approval (for a prevention indication)	1960	2012
No. of subjects whose data were included in application to FDA (for a prevention indication)	897 women	7619 persons
No. of persons on medication prior to FDA approval (for a prevention indication)	<1.5 million woman-years	Nearly 5 million patient-years (on emtricitabine, tenofovir, or emtricitabine-tenofovir)
Median time on medication among subjects whose data were included in the FDA application (for a prevention indication)	<1 y (as only 132 women were on the medication for >1 y)	1–2 y
Monthly cost (\$US 2012)	\$77	\$1425

Abbreviations: FDA, Food and Drug Administration; HIV, human immunodeficiency virus; PrEP, pre-exposure prophylaxis.

McCormick challenge and seed money, Pincus set out to demonstrate that progesterone could block ovulation in humans as it had in rabbits [5].

Before obtaining the funding, Pincus already had a collaboration with Dr John Rock (Figure 4), a Harvard obstetrician-gynecologist. Rock, whose interest ironically was in fertility, had begun work with newly available synthetic progesterone, injecting it into infertile woman to regulate the menstrual cycle [5]. Recognizing the significance of each other's work, the 2 initiated clinical trials of progesterone. By 1955, they demonstrated that many women administered progesterone stopped ovulating, only to resume ovulation once the hormone was discontinued. Within 2 years, the FDA approved the product, manufactured by Searle, as a treatment for menstrual disorders and infertility. Off-label use for contraceptive began immediately with a half-million women using it for this indication by 1959 [5].

A contraceptive indication, however, required additional testing to show longer-term safety and efficacy. But many states, Massachusetts included, prohibited birth control through old laws still on the books. Therefore, study subjects were recruited overseas in Puerto Rico, Haiti, and Mexico. Local newspapers questioned the investigators' credentials and motives, but the study enrolled quickly and few enrollees



Figure 1. Photograph of Margaret Sanger (1916). Smith College Archives (Margaret Sanger Papers), Northampton, Massachusetts. (Image used with permission of the Sophia Smith Collection of Smith College.)

withdrew [4]. Searle's application to the FDA, submitted in October 1959, included data on 897 women taking OCP for 1 to 37 months [5]. On 11 May 1960, following approximately 10 years of development, the first OCP, called Enovid, was born [6] (Figure 5).

PrEP: A MORE NATURAL BIRTH

PrEP experienced a less politically charged inception— at least in the scientific community. Short courses of chemoprophylaxis to prevent infections such as malaria were standard care. Similarly, there was recognition of the importance of advancing biomedical prevention for HIV in the absence of a vaccine or cure [7]. Proof of the PrEP concept with a tenofovir precursor was established in 1995 in macaques [8].

Yet research in humans lagged; it would be a decade before clinical trials were initiated. As with the early contraceptive studies, conducting PrEP studies domestically proved challenging, leading researchers to seek volunteers overseas. In contrast to modest negative press that met work on OCP,



Figure 2. Photograph of Ms. Katherine McCormick. Stanford University School of Medicine, Palo Alto, California. (Image used with permission of Stanford University School of Medicine.)

international PrEP researchers were openly criticized and trials in Cambodia (2004) and Cameroon (2005) were stopped altogether [9]. Yet, beginning in 2004, years before combination emtricitabine-tenofovir (Truvada) was approved for prevention, it was already on the market for treatment. Patients and providers began to consider emtricitabine-tenofovir for HIV prevention [10–12]. Ultimately, studies were conducted and efficacy demonstrated by 2009 [13]; additional results were published in 2012 [14, 15]. Finally, after prolonged deliberation and a delay to allow for review of the proposed risk evaluation and mitigation strategy, the approval for use as prevention was granted on 16 July 2012 [1].

PILLS FOR PREVENTION: HISTORICAL PARALLELS

Safety

Safety is a particular concern when any drug is given to healthy people, especially those of child-bearing age. With OCP, early results suggested only common side effects (eg,

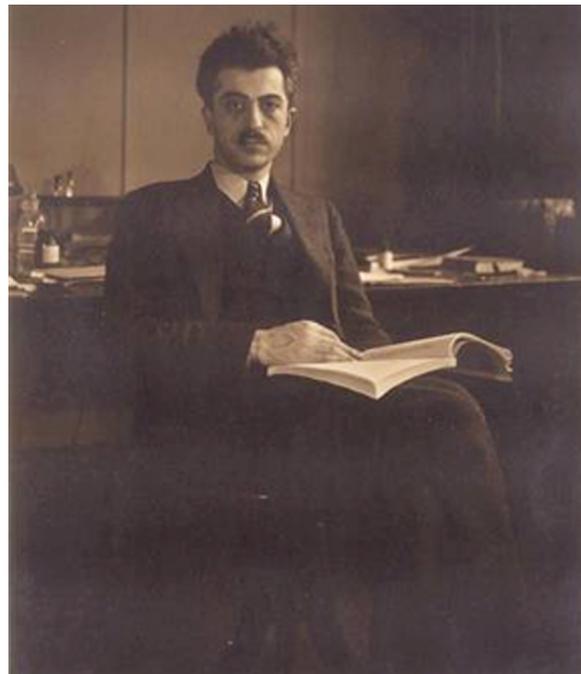


Figure 3. Photo of George Pincus, PhD. University of Massachusetts Medical School Archives, Lamar Soutter Library, University of Massachusetts Medical School, Worcester, Massachusetts. (Image used with permission of the University of Massachusetts Medical School Archives.)

headache, nausea, dizziness). Yet patients and providers were worried about long-term problems [16]. Indeed, the FDA approved Enovid for only 2 years' use [4].

The worries were well-founded. Within a year, Searle collected reports of significant complications, such as venous thromboembolism and stroke in 132 women [6]. These reports culminated in a case-control study published in 1969 that definitively established the risk of thromboembolism [17]. A second major concern, the development of cancer on high-dose hormones, was then a theoretical issue.

In response, work to reduce the hormone dose began, as did exclusion of women who were inappropriate OCP candidates (eg, older smokers) [3]. Congressional hearings were held, a moment that gave focus and voice to the nascent women's health movement. The initial studies were criticized by some feminists and health journalists because researchers had done the work abroad [3] and had submitted data on 897 women observed a maximum of 3 years (801.6 women-years), only 132 of whom had taken OCP continuously for a year or longer [6].

Because of the concern and the high-profile politics involved, the FDA produced something relatively new—the package insert [4]. Both the open hearings and the insistence on provision of detailed information to any woman receiving OCP indicated a basic shift in health care: the patient was

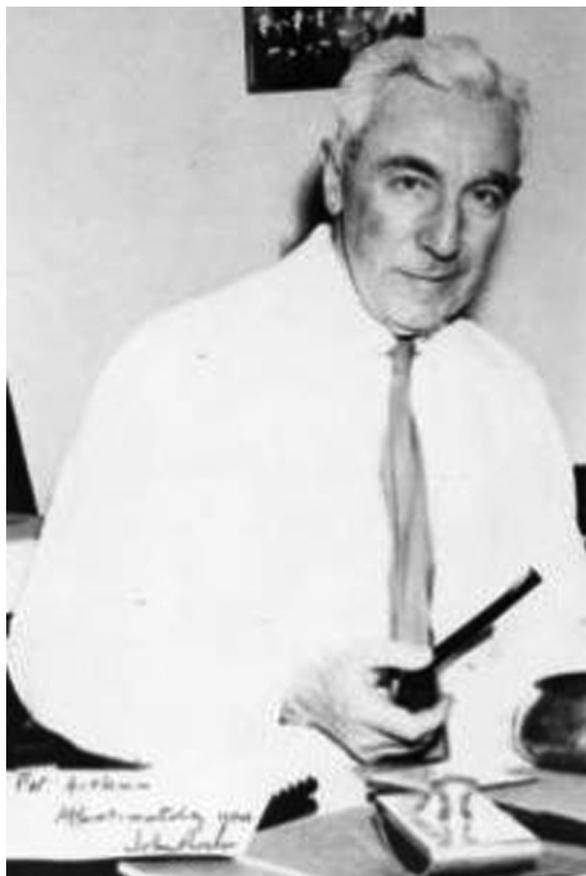


Figure 4. Photo of John Rock, MD. Countway Medical Library, Harvard Medical School, Boston, Massachusetts. (Image used with permission of the Harvard Medical Library in the Francis A. Countway Library of Medicine.)

now a consumer. It would be almost a full decade before the practice of informed consent for medical research became the convention [18].

With PrEP, more data have been amassed on safety over the 8 years of emtricitabine-tenofovir use among millions of HIV-infected patients around the world (3 and 5 million patient-years of use for emtricitabine and tenofovir, respectively [19]). Gilead's FDA application contained data on over 8 times as many patients as did Enovid's. In general, emtricitabine-tenofovir has been safe [20], though the long-term safety profile is not well characterized. As with OCP, low toxicity is necessary because the medication is for healthy, HIV-negative persons [13–15, 21]. Renal and bone toxicities were anticipated based on the experience of tenofovir for HIV treatment [22]; thus far, clinical trials have not found increased creatinine elevations in those taking tenofovir for prevention over a median 1–2 years [13–15]. One PrEP clinical trial found a small but



Figure 5. Original bottle of Enovid, FDA-approved for use as an oral contraceptive pill in 1960. (Image used with permission of Pfizer.)

statistically significant decline in bone mineral density (BMD) among young men. The implication of this finding is uncertain and requires prolonged follow-up [23]. One interesting parallel is that another form of contraception, depot medroxyprogesterone acetate, is also associated with reduced BMD, especially among young women; such declines may be larger than those among emtricitabine-tenofovir users and may not be completely reversible after discontinuation [24].

Similar to OCP, the study population for published emtricitabine-tenofovir trials included few US-born men and very few African-American men. These populations, which may have a higher background rate of renal disease, likely would comprise a substantial population for PrEP [25]. As with other pills, the toxicity profile seen early may underestimate the impact on a larger, less selected population. In parallel, investigation has begun on intermittent dosing [26, 27] and rectal application of tenofovir gel [28], which may improve the safety (and acceptability) of PrEP.

Cost

Financial concerns plagued early efforts to scale-up the use of OCP. The initial monthly price was \$10 [6, 29] (\$77 in 2012, inflation-adjusted) [30]. This relatively high cost, combined with the need to visit a physician to obtain a prescription at least twice annually, created economic and logistical hurdles that only women of the middle or upper socioeconomic classes could overcome [3]. The cost also prohibited many teens from obtaining OCP, although, anecdotally, some pocketed pills from family members [16]. To expand access, Planned Parenthood clinics, using private subsidies, made OCP more affordable; federal subsidies supported widespread use, from an initial pilot of \$8000 in 1964 to \$400 million annually by 1975 [6]. This government support of contraception for poor people, some of whom were minorities, led to accusations of OCP as a “racist tool” foisted on blacks by white officials to limit family size [4]. Though the rhetoric was inflammatory, some early promoters of OCP *did* specifically seek birth control as a form of *population* control to diminish birth rates among “dysgenic types,” ie, poor, uneducated people [31].

Cost is a major issue for PrEP; daily oral emtricitabine-tenofovir for prevention is \$1425 monthly [32]. This estimate does not include additional expenditures for screening, monitoring, physician visits, and support to ensure full adherence [2]. Although some models estimate that this high price would be cost-effective given the lifetime costs incurred by someone with HIV [33], financing remains unsettled. The problem is further complicated by cost containment efforts (including waiting lists) in some states for AIDS Drug Assistance Programs (ADAPs) to treat those already infected.

Anecdotally, some private insurers have begun to cover emtricitabine-tenofovir for this indication, and the manufacturer has established a patient assistance program. But whether federal funders will agree to open coffers for prevention, just not treatment, remains unclear. Some experts worry that, unless public funding is established without cost sharing, PrEP could exacerbate existing health disparities by protecting only those able to afford it [34].

Risk Behavior, Societal Impact

When introduced, and ever since, some have raised the concern that OCP would promote promiscuity. Introducing a product that would allow sex to be “uncoupled” from procreation generated both hope and fear. A decline of moral standards was expected by some but doubted by others [16], including young women themselves [4]. A conservative newspaper warned “the foundations of contemporary sexual morality may be threatened” by OCP [6]. A media storm followed the news that students were prescribed OCP by a college clinic [35]. Yet initial use was primarily among married women who

wanted to limit family size and space children; it took time before use became more common among the unmarried, who found it stigmatizing to admit to *planning* sex (rather than getting swept up in the moment) [3]. Still, there was (and is) no shortage of blame heaped on OCP including the speculative claim that it caused a “sexual revolution.” Such an inference ignores the gradual generational changes in norms about sex over many years [4] and continues despite the fact that “no one ever established a connection between these two phenomena” [4].

The largest conflict occurred within the Roman Catholic Church. Although John Rock maintained a devout Catholic faith and publicly explained the mechanism of action of OCP as mirroring natural physiology, his argument failed to convince Church leaders, including the Vatican. After years of debate, a 1969 encyclical did *not* lift a longstanding ban on the use of contraception. But during the decade-long deliberation within the Church, many American Catholics quietly began to use OCP [4, 6].

No published clinical trials have shown evidence of increased sexual risk behavior while taking PrEP [13–15, 19, 21]. However, concern persists that this may occur outside the clinical trial context. During blinded studies, participants knew they might be receiving placebo and adjusted behavior accordingly, but when prescriptions are given, doubt is removed. Open label studies are ongoing [36] and will help to answer this question. Similar to the shifting societal norms in the 1960s when the OCP was introduced, PrEP has become available at a moment when public attitudes toward homosexuality have moved towards greater acceptance.

Acceptance, Adherence

Leading up to its 1960 FDA approval, many wondered whether women would even take OCP *at all* once available. After all, the idea of a “prevention drug – prevention as a social activity” was novel and untested [6]. There was also widespread class-ism; some experts expected poor women with limited education to be unable to take a daily pill [4]. Even drug companies were incredulous that women would do so, and despite the prospect of profits if proven wrong, they initially balked at marketing this new class of medication [6].

But women and physicians knew the importance of OCP immediately. As noted, even before OCP was approved for contraception, it was being used off-label to prevent pregnancy. Prescriptions rose; users numbered 3.8 million by 1965. Today that number is in the tens of millions. Thanks to private and federal subsidies, women from all socioeconomic strata accepted [6] and adhered to OCP [37]. Drug companies, upon realizing the market potential, also played a role in the growth. They spent large sums on “detail men” who visited physician offices, as well as on advertising, direct mailings,



Figure 6. Advertisement for Enovid in the form of a promotional badge (1961). The front shows Andromeda, a female figure in Greek mythology. She frees herself from chains, symbolizing this new contraceptive. (Badge dimensions: 5.8" × 4.1" × 1.0") (Image used with permission of the Museum of Contraception and Abortion, Vienna, Austria). The reverse contains the following text: "UNFETTERED From the beginning, woman has been a vassal to the temporal demands, and frequently the aberrations, of the cyclic mechanism of her reproductive system. Now, to a degree heretofore unknown, she is permitted normalization, enhancement, or suspension of cyclic function and procreative potential. ENOVID The first comprehensive regulator of female cyclic function - is here symbolized in an illustration from ancient Greek mythology: Andromeda freed from her chains. SEARLE Research in the service of Medicine."

and promotional items (Figure 6). Women learned of the drug primarily from magazines and newspapers, but also radio and television—and from each other [4]. The swell of interest and acceptance served to shift the dynamic in physician-patient relations: Women approached their providers with not just the knowledge of their “problem” (prevention of pregnancy) but also the solution (OCP) [4].

No one knows if PrEP will be as widely accepted by the group who could benefit: sexually active HIV-negative persons. Despite evidence from the pre-approval period showing willingness to participate in clinical trials [13–15, 20] and interest reflected in surveys [38–44], some doubt that interest will persist in “real world” conditions [25]. Furthermore, some experts are concerned that paradoxically, only the “worried well” will accept (and adhere) to the medication [45], while persons at real risk might be less inclined to take a pill daily [25]. Whether marketing can effectively communicate to those who might benefit the most remains uncertain. Among persons participating in clinical trials of oral PrEP to date who are presumably at high risk for HIV acquisition

(Table 2), adherence estimates are heterogeneous [46]. Although adherence (by self-report or pill count) exceeded 80% in these PrEP studies, drug concentration measurements revealed a different reality [46]: in iPrEx, tenofovir levels were detectable in only 54% of a subsample of men [13]; in FEM-PrEP, tenofovir levels were suggestive of consistent use in only 15%–26% of seroconverting women [21]. Women in FEM-PrEP reported low levels of perceived risk, which may have driven the suboptimal adherence [20]. Ultimately, subjects in Partners-PrEP, a study of the PrEP in serodiscordant couples, achieved the highest levels of adherence (97% by pill count) [14], perhaps due to the adherence reinforcing role played by seropositive partners [47]. Seronegative women may benefit particularly from such support given the findings of futility of PrEP in 2 studies in women alone [46].

KEY DIFFERENCES: EFFICACY AND RESISTANCE

Though the similarities are many, there also are key differences between the 2 prevention approaches. First, early trials of OCP showed virtually 100% efficacy [4], an improvement over all other methods (eg, condoms, diaphragm, rhythm method, *coitus interruptus*). Even efficacy during “typical use” of OCP (outside of clinical trial settings) remains above 90% [48]. In contrast, the efficacy of oral PrEP is more difficult to determine but appears lower: even in the context of highly controlled, randomized trials, overall efficacy has not exceeded 80% in any study [13–15, 19, 46]. However, adherence has been shown to be critical in each of 3 trials that measured drug levels, suggesting that PrEP may have a less forgiving adherence-efficacy ratio than the OCP. For example, a re-examination of the data to include only those with detectable drug as “treatment,” very high relative risk reduction in HIV acquisition (84%–92%) is described compared to placebo [49]. Further, combining iPrEx results with data from a pharmacokinetic study of oral tenofovir, PrEP efficacy could theoretically approach 100% [50]. Achievement of high levels of adherence adds to the challenge of implementing widespread emtricitabine-tenofovir broadly [51].

Also concerning is the possibility that this new prevention method will lead some to abandon less acceptable but more effective methods such as condoms [52], so-called risk compensation, exposing them to HIV and other sexually transmitted infections. This parallels what happened toward the end of the first decade of OCP: gonorrhea rates among women rose in the years following its arrival [53], although, as before, blame heaped on the pill was pieced together from circumstantial evidence only and never definitively established.

Second, public health officials involved in the scale-up of emtricitabine-tenofovir harbor concerns about the development

Table 2. Pre-exposure Prophylaxis (PrEP) Trials With HIV Endpoint Findings, Conducted, Completed, or Ongoing to Date

Study	Reference	Active drug/ formulation	Population	No.	Location	HIV reduction point estimate
iPrEX	[13]	Truvada tablets	MSM and transgender women who have sex with men	2499	Peru, Ecuador, South Africa, Brazil, Thailand, USA	44% efficacy
Partners PrEP Study	[14]	Tenofovir tablets Truvada tablets	Heterosexual serodiscordant couples	4758	Uganda, Kenya	67% efficacy tenofovir 75% efficacy Truvada
TDF2 Study	[15]	Truvada tablets	Heterosexual men and women	1200	Botswana	62% efficacy
FEM-PrEP	[20]	Truvada tablets	Women	1950	Kenya, South Africa	Stopped for fertility
MTN-003 (VOICE)	[59]	Truvada tablets Tenofovir tablets Tenofovir 1% gel	Women	5029	Uganda, Zimbabwe, South Africa	Truvada ongoing; Tenofovir tablets and 1% gel stopped for fertility

Table adapted from van der Straten et al [47] with permission.

Abbreviations: HIV, human immunodeficiency virus; iPrEX, pre-exposure prophylaxis initiative; MSM, men who have sex with men; MTN, Microbicide Trials Network; PrEP, pre-exposure prophylaxis; VOICE, Vaginal and Oral Interventions to Control the Epidemic.

of antiretroviral resistance once widespread use for prevention begins [2, 51]. Although resistance was only noted to occur in those with undiagnosed acute infection at the start of the trials (rather than among those with incident infection during the study [19]), the specter of resistance persists [54], particularly in the United States where emtricitabine-tenofovir is in the majority of first-line regimens for treatment-naïve patients [55]. Fear of drug resistance is unique to PrEP; the fear facing those with failure of OCP was pregnancy itself.

BACK TO THE FUTURE?

In 1960, approval of a pill for prevention changed the world. Following an unusual beginning, borne of visionary investment by women and development by a doctor interested in fertility, OCP survived a decade of controversy about its safety, cost, impact on risk behavior and society, and acceptability to become an essential part of daily life. About 82% of US women report taking OCP at some point in their lives [56].

This experience could and should inform implementation of PrEP. As detailed, the parallels are many. Adherence experts have begun to use the OCP experience to map out an optimal strategy [57]. While safety seems promising for emtricitabine-tenofovir, we should expect some surprises as use is scaled up to populations who were not included in the clinical trials. In addition, although careful surveillance of ongoing sexual behavior after the launch of emtricitabine-tenofovir is appropriate, longer-term societal trends were established long before emtricitabine-tenofovir entered the market; similar to OCP, changes in behavior should not automatically be blamed on the new HIV prevention pill. Finally, this expensive

medication can only reach those in need, limiting disparities, if public funding is secured, as it was for OCP.

The implementation of PrEP is rapidly evolving, as occurred 50 years ago with OCP. Researchers are already exploring intermittent dosing and other drugs [58]. And, as with contraception, the future of PrEP will probably not be one of pills, at least not for everyone. Newer hormone delivery methods (eg, vaginal rings, depot preparations) are paralleled by similar delivery devices for antiretrovirals in development. In this context, an ongoing, thoughtful approach to implementation, bearing in mind the historical insights gained from the 1960s, might serve as well as we begin this new chapter in the control of HIV.

Note

Potential conflicts of interest. Both authors: No reported conflicts.

Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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