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Antivirals for the treatment of Monkeypox: utilization in the general and HIV-positive population and gaps for research. A short narrative review

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SUMMARY

Monkeypox (Mpox) is an emerging viral disease caused by the monkeypox virus (MPXV), a double-stranded DNA virus member of the genus Orthopoxvirus, first reported in humans in 1970. Since May 2022, a global spread of the infection has occurred that the World Health Organization (WHO) declared a public health emergency. In view of the global threat, efforts have been devoted to bolstering the disease spread as well as identifying viable therapeutic modalities. People living with HIV may be at an increased risk of adverse outcomes and may require antiviral treatment. With regard to antiretroviral drugs agents, the anticipated adverse drug reactions do not preclude the co-administration of combined antiretroviral therapy and antivirals for mpox. More data on treatment recommendations and efficacy in patients with immunodeficiency due to HIV is needed. In this review, tecovirimat, cidofovir and brincidofovir - antiviral agents with activity against MPXV and other Orthopoxviruses are reviewed, their utilization in vulnerable patient groups affected by mpox such as people living with HIV and possible gaps for future research. Tecovirimat is an inhibitor of the Orthopoxvirus VP37 envelope wrapping protein thus rendering enveloped virus formation impossible. Cidofovir and its prodrug brincidofovir interfere with DNA synthesis through DNA polymerase inhibition. Ongoing research is intensified to verify efficacy and applicability.

Keywords: Monkeypox, tecovirimat, brincidofovir, cidofovir, HIV, antiretroviral therapy.

INTRODUCTION

Mpox, caused by the monkeypox virus (MPXV), a double-stranded DNA virus member of the genus Orthopoxvirus, was first isolated in 1958 in Denmark in captive primates (Macaca cynomolgus), hence the coined term "monkeypox". It was not until 1970, near the end of smallpox eradication endeavours, that animal-to-human transmission was reported in a 9-month-old child in the former Zaïre (now The Democratic Republic of Congo) [1-3]. Nowadays, person-to-person transmission is rare, but is becoming more frequently encountered, possibly due to the lack of cross-immunity following variola virus vaccination, which was not widely administered after smallpox eradication [4]. The first identified outbreak outside Africa in the USA in 2003 was linked to imported infected animals [5]. Since May 2022, a global outbreak of mpox has occurred involving approximately 110 countries, of which 103 have not histor-

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ically reported mpox. The World Health Organization (WHO) has declared the mpox outbreak a public health emergency as a result of the outbreak's extraordinary rate of spread [2, 3]. Public health authorities have adopted rigorous protocols and case definitions to guide early recognition of mpox cases [6]. Not only is early identification conducive to halt disease spread but also to discern patients at high risk for complications who require treatment [7]. Yet, this process has been hindered by the fact that so far only the descriptive studies conducted in Africa have provided most of the data for our understanding of human disease [2]. Notably, the paucity of data on effective treatment in particular is a subject to be examined minutely. The review aims to present a clinically oriented analysis of the available data on primary approved and available therapeutic modalities in Europe and the USA, their utilization in vulnerable patient groups affected by mpox such as people living with HIV and possible gaps for future research.

MATERIAL AND METHODS

For the purpose of the present scientific paper, a descriptive narrative review format was implemented. A search was conducted on the PubMed/MEDLINE library database based on the following keywords: monkeypox, MPXV, antivirals, tecovirimat, brincidofovir, cidofovir, antiretroviral therapy, HIV. The search was restricted to reviews published between 1991 and 2023. Prior to submission a consecutive search was carried out to incorporate any newer data published in the interim.

The below listed antiviral drugs were identified with known activity against mpox, becoming the review subject. Tecovirimat is the first drug of choice for the treatment of mpox, the alternatives being cidofovir and brincidofovir.

Viral life cycle and clinical significance

Poxviruses present a sophisticated morphogenesis cycle generating antigenically distinct viral particles [8]. Understanding it plays a crucial role in identifying the steps at which interference can be accomplished to halt viral replication and/or assembly (Figure 1).

Poxviruses produce two mature forms, both of which are instrumental in mediating infection: intracellular mature virus (IMV) and intracellular enveloped virus (IEV), which is subdivided into a cell-associated enveloped virus (CEV) and extracellular enveloped virus (EEV) but are morphologically indistinguishable [3, 9].

Upon entry, viral uncoating, transcription and translation are initiated – processes that occur in autonomous intracytoplasmic structures (virus

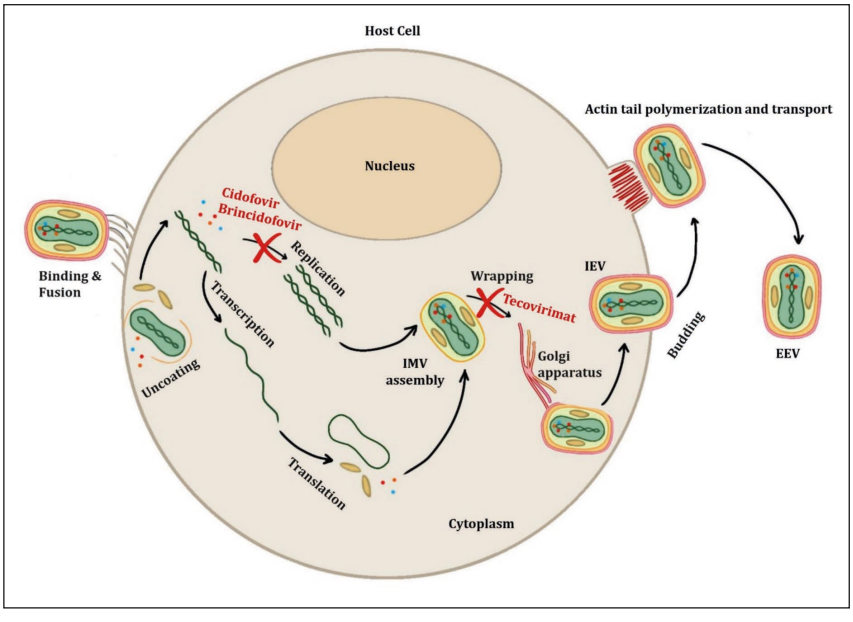

Figure 1 - Replication cycle of a poxvirus and mechanisms of action of Orthopoxvirus antivirals. Consult text for further explanation.

factories) independent of the nucleus. The viral assembly then commences with membrane crescents and immature virions (IVs) that contain the genome, structural and non-structural proteins that further undergo conformational changes and form mature virions (MV) [8]. The vast majority of these already infectious virions remain intracellularly until some are transported via microtubules to be subsequently processed and acquire an additional outer lipid membrane bilayer originating from the trans-Golgi network and the early endosomal cisternae. The thus-formed enveloped virions (EVs) are also called intracellular enveloped virions (IEVs) [8, 10, 11] (Figure 2). The EV consists essentially of an MV with at least nine viral proteins (A33, A34, A36, B56, B5, E2, F12, F13, K9) that differentiate it from the MV and adapt it for immune evasion [9, 10, 12]. A33, A34, A56, B5, and K2 undergo glycosylation and are expressed on the outer envelope surface, whereas F13, indispensable for wrapping, undergoes acetylation (palmitoylation) and is on the inner envelope surface [10].
Following wrapping, IEVs migrate to the cell periphery and fuse with the cell membrane, resulting in the release of EEV. IEVs that remain attached to the cell surface are now CEVs that can initiate actin polymerization and actin tails formation, a process dependent on the A33, A34 and A36 presence on the outer envelope. CEV can be propelled by actin tails toward an adjacent uninfected cell or be forced out of the cell surface [13]. In contrast, EEVs are thought to be responsible for early distal dissemination [3, 9, 11].

Merely a small portion of the aforementioned and other viral poxvirus proteins can be exploited as a biological target. The F13 protein is one such target of the antiviral tecovirimat.

Clinical considerations in managing mpox in people with HIV and therapeutics

The current global outbreak has disproportionately impacted on HIV-positive individuals, most of them men who have sex with men (MSM) with up to 49% being HIV-seropositive among those with known HIV status [14, 15]. Persons living with HIV and particularly those with advanced and poorly controlled disease who have mpox may be at greater risk for severe disease. HIV-infected patients are more susceptible to developing more generalized and confluent or partially confluent rash, secondary bacterial skin infection, genital ulcers, longer duration of illness as well as new and uncommon clinical presentations such as tonsillitis, rectal pain due to proctitis and penile oedema as opposed to HIV-negative mpox cases [5, 16]. Most reported deaths have heretofore been in children and people with HIV who were not virologically suppressed [17]. This gives rise to the necessity for a comprehensive and balanced assessment of both viral suppression and CD4 count in evaluating the extent of immunosuppression and the inherent risk of severe outcomes. Notwithstanding the lack of sufficient and definitive data to delineate exact criteria for risk assessment, patients with HIV infection, particularly those with a low CD4 count (<350 cells/mm3) or in the absence of

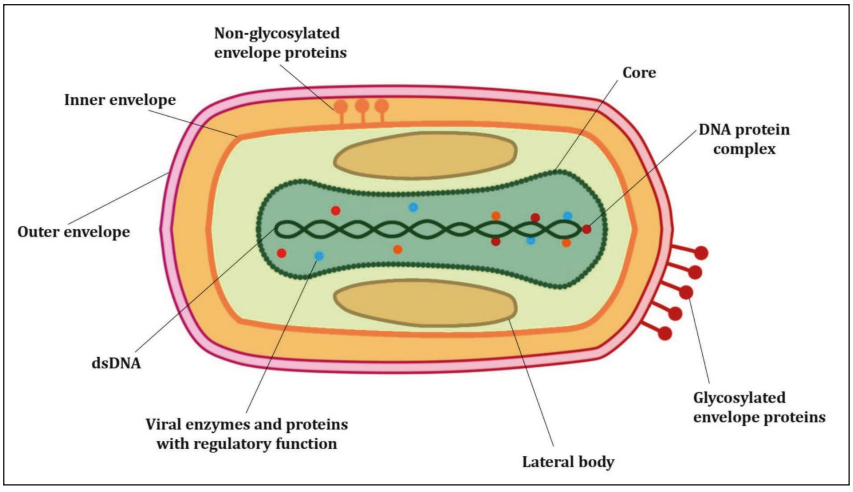

Figure 2 - Structure of an bilayer enveloped Orthopoxvirus. Consult text for further explanation.

viral suppression, are to be considered at higher risk of developing severe mpox and complications. People living with HIV receiving antiretroviral therapy (ART) and who are subsequently virologically suppressed are not considered immunocompromised [5, 18].

For persons living with HIV diagnosed with mpox, ART and opportunistic infection prophylaxis must not be discontinued. HIV pre-exposure prophylaxis (PrEP) or post-exposure prophylaxis (PEP) should also be continued in an orderly fashion. In the case of patients with newly diagnosed HIV infections simultaneously with mpox diagnosis, initiation of ART is recommended at the earliest possible time following a confirmed HIV diagnosis [5, 18]. Pharmacokinetic drug interactions between ART and mpox antivirals have to be considered should treatment of mpox in persons with HIV infection be deemed necessary on account of risk factors. Combinations of antiretroviral therapies from different medication classes are given to control HIV virus replication and reduce the risk of developing resistance. Preferred ART regimens should consist of one of the following combinations - 2 NRTIs (nucleotide reverse transcriptase inhibitors) plus 1 NNRTI (nonnucleoside reverse transcriptase inhibitors), 2 NRTIs PLUS 1 PI (protease inhibitors), 2 NRTIs PLUS 1 INI (integrase inhibitors) - as a backbone therapy.

Tecovirimat

Tecovirimat is the only antiviral medication approved by the European Medicines Agency (EMA) for the treatment of mpox in the EU. The medicine has been authorized under "exceptional circumstances", and, as such, it is subject to pharmacologic vigilance and additional monitoring [19]. Tecovirimat has been approved by the Food and Drug Administration (FDA) for smallpox treatment with the specification that the drugs developed to treat smallpox may be used to treat mpox off-label designating that the approved drug is used for an unapproved indication or population [20]. This fact imposes the requirement of obtaining informed consent prior to tecovirimat initiation [21]. Tecovirimat has activity against Orthopoxviruses by inhibiting the Orthopoxvirus protein VP37, a major envelope protein and a structural homologue of protein F13, which is involved in the process of an enveloped virion formation upon viral release by the host cell [2, 22] (Figure 1). Enveloped virions are pivotal in distal hematogenous dissemination and transmission to adjacent cells [13]. Tecovirimat does not inhibit DNA replication and translation, nor the assembly of mature viruses [2, 23].

Treatment with tecovirimat should be initiated as early as possible after establishing the diagnosis [2, 23] (Table1). No dose adjustment is required in case of renal and hepatic impairment during treatment with tecovirimat capsules. However, caution is advised in the use of the medication in these specific populations [23]. Treatment with IV tecovirimat could also be considered, for example, in the case of critically ill patients. For the time being, it has not been authorized by EMA. There are no absolute contraindications for the use of tecovirimat capsules except hypersensitivity to the active molecule. In regard to IV tecovirimat, its application is contraindicated in patients with renal failure whose creatinine clearance falls below 30 mL/min. Renal toxicity is expected in this specific group due to the excipient hydroxypropyl-β-cyclodextrin eliminated through glomerular filtration. Significant drug interactions include hypoglycaemia when tecovirimat is co-administered with the type 2 diabetes oral agent repaglinide. Such patients should be monitored for hypoglycaemic episodes [21].

Tecovirimat and ART

Tecovirimat is a weak inducer of CYP3A. Thus, some interactions may result in a reduction in certain antiretroviral levels. No clinically significant drug interactions are expected with NRTIs and the INIs bictegravir, cabotegravir, dolutegravir and raltegravir. The same applies to elvitegravir, and no dose adjustments are recommended. However, tecovirimat co-administration with elvitegravir boosted with cobicistat (EVG/COBI) may cause potential reductions in serum concentrations. Potential reduction in NNRTI, PI and the CCR5 antagonist maraviroc levels is anticipated during concomitant administration with tecovirimat, but no dose adjustment in either drug is necessary. Even so, in treatment-naïve patients on tecovirimat, initiation of an ART regimen with rilpivirine should be delayed for two weeks after tecovirimat course completion, or the addition of oral rilpivirine could be considered for patients who have recently begun therapy. For treatment-experienced patients, no adjustment is required [25, 26]. In-

deed, a growing body of empirical evidence tends to favour the application of tecovirimat in patients on ART [24].

In the matter of multidrug-resistant HIV-1 infection, treatment with the attachment inhibitor fostemsavir (FTR) or the capsid inhibitor lenacapavir (LEN), both CYP3A4 substrates, tecovirimat could potentially decrease serum concentrations due to CYP3A4 induction. For the time being, the clinical relevance is unknown, but dose adjustments are not recommended [5, 25, 26]. Ultimately, given the rarity of the expected and identified adverse interactions with ART therapy for HIV, co-administration of tecovirimat and ART should not be impeded [5].

When treatment with tecovirimat is impossible on account of contraindications or after disease progression/relapse despite tecovirimat therapy, alternative antivirals could be used for mpox treatment.

Cidofovir

Cidofovir has a broad spectrum of activity against DNA viruses [27]. It is an acyclic nucleotide analogue of cytosine (acyclic nucleoside phosphonate) that selectively inhibits viral DNA polymerases in infected cells (Figure 1). Intracellularly, cidofovir undergoes phosphorylation, which is not dependent on viral or cellular enzymes, to cidofovir diphosphate. Cidofovir demonstrates greater selectivity for viral DNA polymerases compared to human DNA polymerases and hinders DNA synthesis by incorporating cidofovir diphosphate in the nascent DNA strand [28]. Given the long half-life of cidofovir metabolites, they may serve as an intracellular drug reservoir, thus possibly interfering with infection and DNA synthesis [27]. Cidofovir is indicated for the treatment of cytomegalovirus retinitis in adults with acquired immune deficiency syndrome without underlying kidney disease. Morever, effectiveness against Orthopoxviruses has been demonstrated in *in vitro* and *in vivo* studies [5]. Successful treatment it's redundant of mpox with cidofovir has been reported on several occasions in the ongoing outbreak [29, 30] (Table 1).

Owing to its low oral bioavailability, cidofovir must be administered as an intravenous infusion at a constant rate over an hour using a controlled-infusion pump. Induction therapy with 5 mg/kg once weekly for two consecutive weeks is followed by a maintenance dose of 5 mg/kg once every other week. The significant adverse reaction profile includes nephrotoxicity and myelosuppression. To minimize renal toxicity, patients must be premedicated with oral probenecid and be adequately hydrated [28].

Cidofovir and ART

Inasmuch as cidofovir exhibits nephrotoxicity, coadministration with other nephrotoxic agents poses a risk of renal insufficiency, proximal renal tubulopathy or Fanconi syndrome [28]. Coadministration of cidofovir with the NRTI tenofovir disoproxil fumarate (TDF) is not recommended. Nephrotoxicity is less likely to occur with tenofovir alafenamide [25, 26].

To alleviate nephrotoxicity, cidofovir is co-administered with probenecid that increases zidovudine (ZDV) plasma levels considerably; hence, zidovudine should either be temporarily discontinued or decreased by 50% on the day of cidofovir-probenecid infusion to avoid zidovudine-induced bone marrow suppression [25, 26, 28].

Drug interactions are unlikely when administering cidofovir with an antiretroviral drug of a different class than NRTI [25, 26].

Brincidofovir

Brincidofovir is an FDA-approved therapeutic agent for the treatment of smallpox and was granted orphan designation status by EMA. As such it is intended for use against rare conditions such as cytomegalovirus retinitis, smallpox and adenoviral disease in immunocompromised individuals [31-33]. Like cidofovir, brincidofovir is also a nucleotide analogue that blocks DNA synthesis through DNA polymerase inhibition [2, 34] (Figure 1). Brincidofovir, a lipid conjugate derivative of cidofovir monophosphate, is a prodrug. The lipid conjugate accounts for better absorption by enterocytes and lipid membranes of target cells. An effective intracellular concentration is achieved after hydrolysis and subsequent phosphorylation to cidofovir diphosphate. An off-label indication is an MPXV infection (Table 1). Brincidofovir has an improved renal safety profile over cidofovir with primarily gastrointestinal adverse events [35, 36]. However, performing liver function tests is recommended in all patients undergoing treatment with brincidofovir due to reported associations with reversible hepatotoxicity [34].

Brincidofovir and ART

Drug interactions between brincidofovir and NRTI, NNRTI, INI, maraviroc and lenacapavir are unlikely. However, when brincidofovir is co-administered with TDF and ZDV, monitoring for nephrotoxicity and blood dyscrasias, respectively, is required [5].

Brincidofovir has clinically relevant drug interactions with protease inhibitors, cobicistat with boosted EVG/COBI and FTR with resultant brincidofovir serum concentrations increase. If PIs, cobicistat, or FTR are co-administered with brincidofovir, brincidofovir-related adverse events, such as LFT elevations, hyperbilirubinemia, diarrhoea, nausea, vomiting and abdominal pain, are likely to occur. Postponement of PI or EVG/COBI dosing for at least 3 hours after brincidofovir administration is recommended [25, 26, 34].

Adjuvant pharmacotherapy

Certain medications serve as an adjunctive antiviral therapy to mpox in the context of aberrant infections. These represent cases of inadvertent viral inoculation in the eye, mouth, genitals, anus, where vaccinia infections pose potential health hazards [37]. Ocular involvement may range from blepharitis, conjunctivitis, keratitis, corneal ulceration and scarring to vision impairment and possibly loss of vision [38]. Hence, it is advisable to incorporate topical ophthalmic preparation of trifluridine in addition to systemic antiviral therapy [39]. Trifluridine is a nucleoside analogue structurally similar to thymidine. As such, it prevents thymidine from being incorporated into viral DNA, leading to defective DNA synthesis and rendering the virus unable to replicate further. Trifluridine has activity against HSV-1, HSV-2, and vaccinia viruses [27]. Topical application of corticosteroids alone for the management of inflammation is discouraged due to the risk of corneal damage exacerbation [40].

DISCUSSION

So far, the effectiveness of tecovirimat for the treatment of smallpox disease has not been determined in humans because adequate and well-controlled trials have not been feasible. Additionally, it is unethical to induce smallpox in humans in order to examine the medication's effectiveness [41]. Moreover, based on research showing lower efficacy in immunocompromised animal models, tecovirimat efficacy in immunodeficient individuals may be decreased [41]. Admittedly, the available empirical data is insufficient to draw a generalised conclusion on the basis of small patient samples regarding the effectiveness of tecovirimat in patients in general and in patients on ART. Despite limitations

Table 1 - General characteristics of tecovirimat, cidofovir and brincidofovir.

	Tecovirimat	*Cidofovir*	*Brincidofovir*
Mechanism of action	Inhibitor of the Orthopoxvirus VP37 envelope wrapping protein	DNA polymerase inhibitor	DNA polymerase inhibitor
EMA approval	Poxviridae Infections, Smallpox Cowpox, Vaccinia Monkeypox	No	No - Orphan drug designation
FDA approval	Smallpox	CMV retinitis	Smallpox
Dosing	PO: 13 kg-24 kg: 200 mg bid; 25 kg-40 kg: 400 mg bid; >40 kg: 600 mg bid; IV: 3kg-35 kg: 6 mg/kg bid over 6 hours; 35 kg-120kg: 200 mg bid over 6 hours; >120 kg: 300 mg bid over 6 hours	PO: Not available IV: 5 mg/kg once weekly	PO: <10 kg: 6 mg/kg/dose once weekly in 2 doses (on days 1 and 8); 10 kg - 48 kg: 4 mg/kg once weekly for 2 doses (on days 1 and 8); >48 kg: 200 mg once weekly for 2 doses (on days 1 and 8) IV: Not available
Course duration	14 days	2 consecutive weeks	2 consecutive weeks
Renal toxicity	IV Tecovirimat is contraindicated if CrCl < 30 mL/min	Possible. Adjust dose accordingly	No
Hepatic toxicity	No	No	Possible. Adjust dose accordingly

Abbreviations: PO, per os (by mouth); bid, bis in die (twice daily); IV, intravenous; CrCl, creatinine clearance.

such as early identification and treatment initiation, clinical benefits could be inferred and would have to be further evaluated. Notably, treatment was well tolerated in small scale studies [24].
In contrast, current data strongly implies that brincidofovir may trigger liver injury. The actual significance of this risk is unclear and warrants additional research and observation [42]. Indeed, in a small retrospective observational study in the UK between 2018 and 2021, all patients treated with brincidofovir demonstrated hepatotoxicity that led to therapy discontinuation. One patient treated with tecovirimat experienced no adverse reactions corroborating the better safety profile [17].
Above all, the current transmission among MSM in non-endemic regions alludes to putative sexual transmission. Thus, understanding mpox in the context of co-infection and, in particular, with HIV is a matter of priority [43]. Additional findings are imperative regarding the effects of therapy on monkeypox in people with uncontrolled HIV infection, given the potential frailty due to severe impairment of adaptive immune responses.
Finally, although monkeypox is not a new disease, the dire need for promising and proven therapies did not become apparent until it was declared a global public health concern. Ongoing investigation under several randomised controlled trials in high-income regions now aims to evaluate the effect of the available antivirals. Be that as it may, extrapolation of these end results to endemic regions, where mpox treatment and drug availability were grossly neglected until recently, would be erroneous, bearing in mind that the viral clade, along with transmission routes, population, and clinical course, differ fundamentally [44]. Separate trials conducted locally are required, and last but not least, the socioeconomic aspects and impact have to be addressed, given the disparity between low or middle-income countries and high-income countries.

CONCLUSIONS

In light of the current mpox outbreak, Orthopoxviruses demonstrated that these outbreaks could be a cause for growing and widespread public health concerns. The opportunity to exploit the available, viable therapeutic options should be grasped. The favourable tolerability of tecovirimat and brincidofovir in patients, as opposed to cidofovir, is an auspicious start. Therefore, randomised controlled trials both in high-income and low or middle-income countries have to be conducted for the foreseeable future to eliminate doubts about efficacy and ascertain utility. Furthermore, these antivirals should be studied more extensively, not only in the general population but also in patient groups at the highest risk of complications due to mpox infection such as people living with HIV. Finally, research on novel therapies and assessment of future scientific needs are imperative to be carried out.

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Conflicts of interest
The authors declare no conflict of interest in regard to this work.

Contributions
DI acquired and synthesised information, wrote the original draft, and edited the manuscript. TV, YS and RA were involved in reviewing, editing and finalizing the manuscript. Yoanna Vasileva designed and drew the figures.

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