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Review

A timeline of reckoning: Tracking the historical rise of antimicrobial resistance across HIV, TB, and malaria

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ABSTRACT

Antimicrobial resistance is one of the major health challenges of this century. Here, we provide an in-depth perspective on the evolution of antimicrobial resistance in three globally relevant infectious diseases, HIV, tuberculosis (TB), and malaria. Specifically, we scrutinize the timelines between deployment and the subsequent emergence of resistance for all drugs that have been mobilized in the fight against these three diseases. Our data reveals that malaria exhibits a slower rate of resistance development to monotherapies in comparison to HIV and TB. While the adoption of combination therapies significantly reduces the risk of *de novo* emergence of resistance, the challenge of pre-existing drug resistance persists, necessitating continuous surveillance and emphasizing the critical need for diverse and innovative approaches to manage and mitigate the ever-growing threat of antimicrobial resistance.

1. Introduction

Modern advances in antimicrobial agents for the treatment and management of infectious diseases have been vital to the improvement of global public health. These agents have revolutionized the healthcare landscape, enabling childbirth, cancer chemotherapy, medical and dental procedures, as well as surgical operations, to occur with significantly reduced risks of life-threatening infections. However, antimicrobial resistance (AMR) is threatening to nullify these remarkable gains through the emergence of "superbugs" that are resistant to many (and in some cases all) of our available treatments [1]. The impact of these "superbugs" is easily exemplified by methicillin-resistant *Staphylococcus aureus*, a common nosocomial infection, which has been shown to increase the mortality of patients by up to 64% compared to those infected with non-resistant strains [1]. In a broader scope, predictive statistical models drawn from 400 million individual records estimated that exclusively bacterial AMR contributed to 5 million deaths in 2019 [2]. Moreover, taking into account viral, fungal, and parasitic diseases, projections indicate that the annual fatality rate attributed to AMR will exceed 10 million by 2050 [3]. In addition to the toll on human lives, there is growing concern about the socioeconomic impact of AMR. A recent report by the World Health Organization (WHO) warns that AMR could impose a staggering 100 trillion USD cost on the global economy by 2050, while the World Bank estimates that over 20 million people may fall into poverty by 2030 due to escalating medical expenses related to AMR [4]. Using a variety of statistical modelling tools based on hundreds of millions of cases over the recent years, a comprehensive 2024 study forecasted that an estimated 8.22 million deaths associated with AMR could occur globally yearly in 2050 [5]. Cumulatively from 2025 to 2050, this would represent a staggering 169 million (145–196) deaths associated with AMR, with the highest burden being carried by south Asia, southeast Asia, east Asia, Oceania, and sub-Saharan Africa, although the developed world would also suffer significant impact [5].

AMR is widespread problem and is implicated across essentially all pathogens against which anti-infectives have been deployed [1]. This review focuses on those colloquially termed "the big

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Table 1
Origins for common and currently used classes of antimicrobial compounds.

Antimicrobial drug class	First compound	Isolated from	References
Aminoglycosides	Streptomycin	*Streptomyces griseus* (soil bacteria)	[94]
Antifolates	Proguanil	Synthetic	[95]
Artemisinin derivatives	Artemisinin	*Artemisia annua (*plant extract)	[96]
Carbapenems	Olivanic acid	*Streptomyces olivaceus* (soil bacteria)	[97]
Cephalosporins	Cephalosporin C	*Acremonium strictum* (soil fungi)	[98]
Glycopeptides	Vancomycin	*Amycolatopsis orientalis* (soil bacteria)	[99]
Lincoamides	Lincomycin	*Streptomyces lincolnensis* (soil bacteria)	[100]
Macrolides	Erythromycin	*Saccharopolyspora erythraea* (soil bacteria)	[101]
Penicillins	Penicillin	*Penicillium* genus (soil fungi)	[102]
Quinolines	Quinine	*Cinchona* genus (tree bark)	[72]
Sulfonamides	Prontosil	Synthetic	[103]
Tetracyclines	Chlortetracycline	*Kitasatospora aureofaciens* (soil bacteria)	[104]
Nitroimidazoles	Azomycin	*Streptomyces eurocidicus* (soil bacteria)	[105]

three": Human Immunodeficiency Virus (HIV), tuberculosis (TB), and malaria. These diseases collectively account for almost 300 million infections per year and cause up to 3 million deaths, earning them a place amongst the deadliest human pathogens [6,7]. Concerningly, this high level of mortality is occurring whilst we still have access to effective treatments. In the face of escalating AMR, global initiatives like the Global Fund have assumed critical importance in combating the relentless rise of drug resistance. As the number of effective last-resort antimicrobials continues to decline, these initiatives play a pivotal role in preserving treatment options. Consequently, there is an urgent need for coordinated research endeavours to unravel the intricate mechanisms of AMR and to develop novel and innovative therapeutics. By doing so, we can prevent a regression to the challenging pre-antimicrobial era and safeguard global health.

A comprehensive review of the molecular mechanisms of resistance and current strategies to combat AMR in HIV, malaria and tuberculosis was published recently. Here, our purpose is to provide a complementary historical perspective [8]. By tracing the development of resistance from the initial introduction of antimicrobials to present-day challenges, we offer insights into how we have arrived at the current state of AMR and underscore the importance of continued innovation and adaptation in our therapeutic strategies. We also present an analysis of the data that shows that resistance is on average faster to emerge for drugs against HIV and TB than it is for antimalarials, and discuss possible explanations for this difference.

2. The antimicrobial crisis: Causes and lessons to be learned

2.1. Factors driving antimicrobial resistance acquisition

AMR is an inherent consequence of microbial evolution, occurring independently of human intervention. Throughout the history life, various animals, plants, fungi, and bacteria have evolved to produce antimicrobial compounds, which form the foundation of many modern medicines (Table 1). Consequently, it is not surprising to find that bacterial samples retrieved from 30,000-year-old permafrost and historically isolated sites exhibit resistance to antibiotics spanning numerous drug classes. This includes those considered last-resort drugs, such as daptomycin, a cyclic-lipopeptide antibiotic [9]. While AMR is a natural process, the misuse and overuse of antimicrobial compounds in human and veterinary medicine have significantly accelerated the rate at which resistance emerges [10]. This widespread use has exerted substantial evolutionary pressure on microbial populations, favouring the survival and proliferation of pre-existing resistant pathogens.

In human medicine, AMR is exacerbated by the overuse of therapeutics, drug misuse resulting from incorrect diagnosis, and non-compliance with recommended treatment durations. A study conducted in Nigeria highlighted the extent of improper antimicrobial use, where malaria treatments were dispensed to symptomatic individuals with suspected, but unconfirmed, malaria infection. Subsequent microscopic analysis revealed that fewer than 10% of these cases exhibited identifiable malaria parasites, underscoring the necessity of confirming infection prior to treatment [11]. Likewise in agriculture, excessive use of antimicrobial agents stands out as a major factor driving AMR. Of note, agriculture is responsible for 80% of the consumption of medically important antibiotics, and within this significant fraction, the primary intent is not to safeguard animal health but rather to accelerate growth [12]. Extensive research, supported by meta-analyses commissioned by the WHO, highlight the considerable impact of moderating and banning growth-promotion antibiotic use in this sector. Such regulation can substantially cut the risk of bacterial resistance in agriculture by up to 39%, while also significantly lowering the frequency of multi-drug resistant bacteria by over 30% [13]. While numerous countries have taken steps to prohibit the use of antibiotics for animal growth promotion, the practice persists in other jurisdictions [14]. Addressing the inappropriate deployment of antimicrobials—whether in human medicine or agriculture—is one crucial step towards combating AMR and preserving the effectiveness of existing treatment options.

2.2. The paucity of anti-infective drug development over the recent decades

In the past several decades, the landscape of anti-infective drug approvals has seen marked fluctuations across various classes of pathogens, as depicted in Fig. 1. The urgency surrounding the HIV pandemic fuelled a sharp uptick in antiviral approvals during the 1990s [15]. In contrast, the early 2000s saw a dwindling pipeline for antibacterials, partially due to the retreat of major pharmaceutical companies from the sector [16]. Novel antiparasitic agents have been notably scarce, a phenomenon largely attributed to their classification under the WHO's category of "Neglected Tropical Diseases" which predominantly affect economically disadvantaged regions [17]. Although the most recent decade saw an increase in both antibiotic and antiviral compounds, the concerning decline in overall therapeutic efficacy persists despite this expanded reservoir of new agents. One significant roadblock has been the lack of innovative antibiotics approved between 2010 and 2019; many candidates failed to meet WHO-defined innovation criteria, which demand novel antimicrobial classes, targets, or modes of action—or, at the very least, absence of within-class cross-resistance [18,19]. Exacerbating this innovation gap are financial hurdles that stem from inadequate private investment, and thereby lead to the insolvency of several pharmaceutical ventures [18,20]. A prominent example is Achaogen, which filed for bankruptcy in 2019 despite

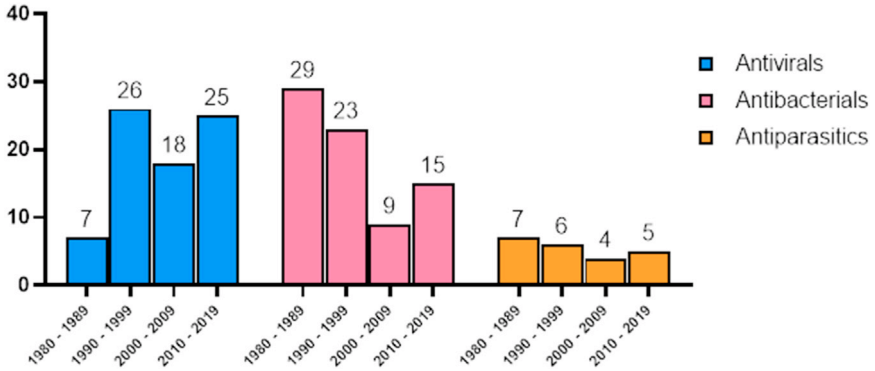

Fig. 1. Temporal trends in approval of anti-infective agents from 1980 to 2019, categorized by therapeutic application (excluding combination therapies). Data adapted and collated from sources: [15,16,106]. The bar graph illustrates the number of approved compounds for the treatment of viral (blue), bacterial (pink), and parasitic (orange) infections for each decade. Antiviral approvals were modest in the 1980s but surged in subsequent decades. Conversely, antibacterial approvals peaked in the 1980s and have been in decline since then. Approvals for antiparasitic treatments have remained consistently low across all four decades.

a decade of clinical trials and obtaining FDA approval for their multidrug-resistant *Enterobacteriaceae* antibiotic [18].

To address the financial challenges in infectious disease research, private-public partnerships have emerged as a crucial source of support, which aims to alleviate financial hardships. Initiatives such as the Medicines for Malaria Venture and Drugs for Neglected Disease Initiative have achieved success in revitalizing the development pipelines for antiparasitic drugs [21]. However, these efforts are disproportionately focused on malaria, leaving diseases like leishmaniasis, Chagas disease, and African trypanosomiasis with insufficient backing for drug development [22]. Mirroring this skewed attention, the landscape of infectious disease research funding has recently witnessed a shift due to the SARS-CoV-2 pandemic, as both public and private sector investments have shifted toward antiviral research, specifically for COVID-19. WHO data from 2017 to 2020 reveals a gradual decline in overall infectious disease research investment, from $4,181 million in 2018 to $3,953 million in 2020, a trend that predates the pandemic but continued through its course [23]. This reduction was observed across various research domains, with vaccine and medicine research and development for diseases other than COVID-19 experiencing noticeable decreases; funding for vaccine research dropped from $1,233 million in 2019 to $1,109 million in 2020, while investment in drug discovery research declined from $981 million to $928 million in the same period [23]. The current situation has significant implications for the aforementioned “big three” diseases, as they now face considerable threats to decades of progress in their control and management due to the pandemic [24]. It is evident that a balanced investment strategy is paramount for a comprehensive approach to fighting infectious diseases, especially considering the variety of pathogens and the necessity for efficacious treatments across multiple disease categories. The uneven allocation of resources, whether driven by specific disease outbreaks or long-standing financial incentives, poses a significant hurdle in our collective fight against antimicrobial resistance.

3. Mechanisms of drug resistance in pathogens

3.1. Viral infections

AMR is a dynamic and complex phenomenon influenced by an interplay of diverse factors, including both the genetic malleability of pathogens and external pressures such as drug exposure. The likelihood of resistance emergence is shaped by multiple factors such as the genetic diversity within the initial pathogen population and the rate of viral replication. For instance, delayed treatment can increase the odds of resistance-conferring mutations being present when therapy finally commences [25]. Regarding replication dynamics, RNA viruses typically outpace DNA viruses, single-stranded forms replicate more rapidly than double-stranded ones, and smaller genomes allow for faster replication [25]. These factors collectively contribute to an accelerated pace of resistance development. Moreover, the absence of proofreading mechanisms in most RNA-dependent RNA polymerases renders RNA viruses especially prone to errors, generating a higher degree of genetic diversity even within a single host. This culminates in the formation of quasi-species, complex populations of closely related but non-identical viral forms, which can harbor mutations that lead to resistance [26]. This is often seen in people with HIV and can result in an accumulation of resistant mutations and, ultimately, treatment failure [27].

3.2. HIV antivirals and rapid emergence of resistance

First identified as the causative agent of AIDS in 1981, HIV has left a lasting mark on global health. Four decades on, the virus has been responsible for an estimated 40 million deaths, while approximately 39 million people live with HIV infection [6]. The extensive health ramifications of HIV triggered an unprecedented response in drug discovery, leading to the remarkable successes of antiretroviral therapy (ART) which have transformed HIV from a fatal disease to a manageable condition [28]. ART significantly extends life expectancy for those living with HIV and also strongly reduces transmission risks, both sexually and from mother to child [29]. The deployment of antivirals as pre-exposure prophylaxis (PrEP) has led to further success, offering substantial protection for people at risk and contributing to a noticeable decrease in new infections in some but not all countries [30]; despite this important contribution of PrEP, the main reason for the global decrease in new infections in ART. As a consequence of widespread uptake of ART for people with HIV and, in some parts of the world, high uptake in PrEP, the number of new infections is declining significantly. Despite these advances, 2023 recorded 1.3 million new HIV infections, with increased cases still being observed in the European and Eastern Mediterranean regions [31,32]. While global strategies by WHO, the Global Fund, and UNAIDS aim to end the HIV epidemic by 2030, considerable challenges around resistance persist [30,33]. The recent deployment of integrase inhibitors (dolutegravir [DTG] and long-acting cabotegravir [CAB-LA]), heralded for their efficacy in treatment and prevention, is now encountering hurdles. Specifically, emerging data reveal that resistance to dolutegravir (DTG)-based regimens occurs more frequently than expected from initial clinical trials [30]. Despite the high efficacy of CAB-LA-based PrEP in preventing infection, integrase resistance could potentially

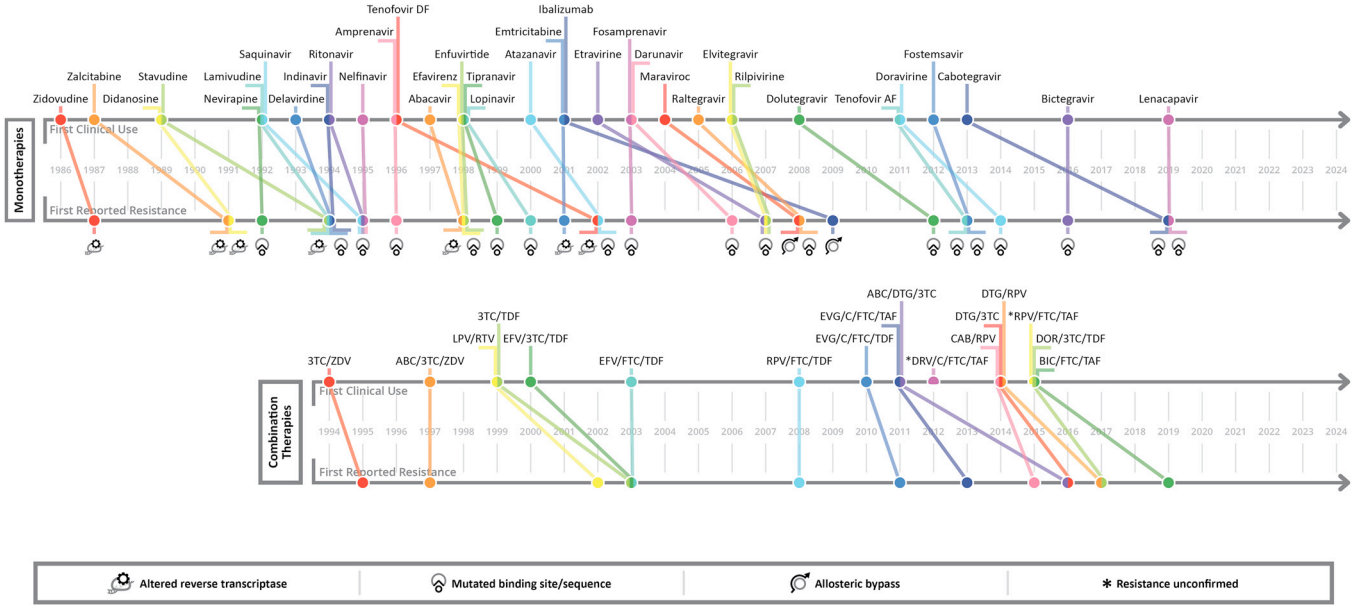

Fig. 2. Year of first clinical use and reported resistance for all deployed monotherapies and combination therapies for the treatment of HIV. Each individual-coloured line links the year either a monotherapy (upper) or combination therapy (lower) was first trialled on HIV positive patients followed by the year resistance was first reported. Combination therapies have been abbreviated to enable better interpretation; lamivudine (3TC), zidovudine (ZDV), abacavir (ABC), lopinavir (LPV), ritonavir (RTV), emtricitabine (FTC), tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF), efavirenz (EFV), rilpivirine (RPV), elvitegravir (EVG), cobicistat (COBI), dolutegravir (DTG), atazanavir (ATV), cabotegravir (CAB), bictegravir (BIC), darunavir (DRV), doravirine (DOR). The mechanism of action for each monotherapy (if known) has been indicated with one of four symbols: (altered reverse transcriptase), (Mutated binding site/sequence), (allosteric bypass). Combinations without confirmed resistance are marked with an asterisk (*).

further increase in the event of insufficient support for timely dosing (see below). These developments reflect the continuous adaptation and need for innovation in HIV treatment and prevention. Detailed in Fig. 2 is the complete timeline and breakdown of the mono- and combination therapies used against HIV since 1987, offering a comprehensive view of these efforts (for compiled data on anti-HIV drugs and drug combinations, see Supplementary Tables 1 & 2).

In the mid-1980s, the development of protease inhibitors gained momentum, aiming at the viral protease that is crucial for the maturation of viral particles. In 1987, another pivotal advance in HIV treatment was gained with the introduction of zidovudine, the first of the nucleoside reverse transcriptase inhibitors (NRTIs) [34]. Far less toxic NRTIs, such as tenofovir and lamivudine, have since been included in many HIV treatment regimens, effectively inhibiting HIV replication by being incorporated into the growing viral DNA chain [35]. In the mid-1990s, the development of protease inhibitors gained momentum, aiming at the viral protease that is crucial for the maturation of viral particles [36]. Shortly thereafter, nevirapine, the first non-nucleoside reverse transcriptase inhibitor (NNRTI), was introduced, offering an alternative approach to impeding viral replication [37]. Unfortunately, resistance to these initial treatments developed within three years (Fig. 2), prompting the shift to combination therapy strategies in 1996. The landscape of HIV treatment continued to evolve with the discovery of entry inhibitors and integrase inhibitors into the early to mid-2000s [38]. These innovations offered fresh hope in the fight against HIV, particularly integrase inhibitors, which demonstrated a more extended period before resistance development, with cabotegravir showing no resistance for up to seven years [39]. First line recommended combination regimens currently include dual NRTIs or NRTIs paired with an integrase inhibitor [32].

Despite the shift to combination therapies in HIV treatment, resistance has remained a persistent issue. During clinical trials of new therapeutics, resistance to monotherapy treatments is often observed, with resistance typically emerging within approximately 2.1 years (σ: 2.1); interestingly, combination therapies still exhibit a quicker emergence of resistance on average, occurring after just 1.8 years (σ: 1.6). Although the difference was not found to be statistically significant (Mann-Whitney U test, $P = 0.96$), it is crucial to consider the underlying factors that may affect this outcome. Before the standardization of combination therapies, the widespread use of monotherapies, primarily with NRTIs like zidovudine, quickly led to resistance in up to one in five new infections [40]. Regimens incorporating early NRTIs have been shown to select for mutations that confer cross-resistance to some or all other NRTIs, for instance, thymidine analogue mutations (TAMs) result in cross-resistance to several other NRTIs, excluding lamivudine and emtricitabine, while the Q151M mutation complex exhibits resistance to all NRTIs [41]. This cross-resistance significantly undermines the efficacy of subsequent combination therapies; when resistance to one component of the therapy is already present, it essentially reduces the combination to a functional monotherapy. For example, when a patient harbors a cross-resistant NRTI mutation in a regimen containing two NRTIs and one NNRTI (e.g. efavirenz, emtricitabine, and tenofovir disoproxil fumarate), the treatment could essentially be seen as a NNRTI monotherapy [42]. To mitigate this risk, current WHO guidelines advocate for resistance testing prior to treatment initiation, allowing for the individual's HIV strain repertoire to be determined [43]. Following this strategy has proven effective for newer drug combinations such as emtricitabine/rilpivirine/tenofovir alafenamide, which has not reported any resistance cases since its 2015 approval when used in patients without pre-existing resistance.

Another advance has been through the use of enhancer drugs such as cobicistat, which, while not active against HIV itself, serves as a pharmacokinetic enhancer to boost the efficacy of other HIV medications, notably some (not all) protease inhibitors [44]. The implementation of such strategies, along with proper therapeutic compliance, has led to sustained effectiveness for combinations such as darunavir, cobicistat, emtricitabine, and tenofovir alafenamide. Given this current success, it is important to note that

a case of complete HIV treatment failure was reported in 2016, prior to the widespread availability of these newer combination therapies. This case involved a 17-year-old girl in Zimbabwe whose HIV infection demonstrated resistance to all available therapeutic classes at the time. While a very rare event, this illustrates the continuous need for innovative therapeutic breakthroughs [45].

3.2.1. Bacterial infections

Bacterial drug resistance is characterized by a broader array of mechanisms compared to antiviral resistance, incorporating both acquired and intrinsic resistance as well as mutational processes. Mutational resistance, akin to viral resistance described earlier, can additionally manifest through mutations in bacterial gene promoter regions. Such mutations can confer adaptive advantages through enhanced efflux pump activity, increased biofilm formation, reduced cell permeability, or the capability to neutralize antibiotics [46]. Horizontal gene transfer serves as another route, enabling bacterial pathogens to acquire drug resistance genes through methods like conjugation, phage transduction, or non-specific DNA uptake from resistant bacteria [46]. The presence of intrinsic bacterial resistance adds further complexity to treatment strategies, as different bacterial species exhibit diverse physiological properties that can render some specific antibiotics ineffective. This is exemplified by the innate resistance of gram-negative bacteria to vancomycin, a phenomenon attributed to the impermeability of their outer membrane [47]. In the subsequent section, we will explore the complexities associated with bacterial resistance by taking a closer look at TB.

3.2.2. The combination of TB therapeutic discovery and inevitable resistance

TB stands as one of the most formidable challenges in global public health, second only to SARS-CoV-2 as a leading cause of mortality from infectious diseases. In 2022 alone, TB was responsible for 1.3 million deaths and an alarming 10.6 million new cases [48]. This disease, caused by the bacterium *Mycobacterium tuberculosis*, has an extensive reach, with an estimated one in four people worldwide having been infected [48]. TB not only imposes an immense burden but also presents intricate challenges for medical intervention. Its complex life cycle, including latent stages and the potential for co-infections with other diseases like HIV, make treatment and management particularly challenging. Moreover, the requirement for extended drug regimens frequently leads to issues with patient compliance, contributing to the ongoing problem of drug resistance. For the timeline and breakdown of the mono- and combination therapies employed against TB since 1944, see Fig. 3; for compiled data on anti-TB drugs and drug combinations, see Supplementary Tables 3 & 4).

In the ongoing battle against TB, the initial introduction of para-aminosalicylic acid (PAS) in 1944 and streptomycin a year later represented significant milestones; they transformed TB from an untreatable condition into a manageable disease [49]. However, within just four years, the emergence of drug-resistant strains revealed the limitations of these early monotherapies [50,51]. Despite these setbacks, these drugs remained extensively used for the management of TB due to the absence of alternative treatments [52]. The field took another leap forward with the identification of isoniazid in 1952, a development that led to the formulation of 'triple therapy'—a regimen that would remain the mainstay of TB treatment for the following 15 years [50,52]. Nevertheless, this new combination faced the same challenge as PAS and streptomycin, with drug-resistant strains being identified within a year of its deployment [53]. The discovery of pyrazinamide, ethambutol, and rifampicin led to more sophisticated treatment strategies. These drugs, combined with isoniazid, have been used together since 1974 and still constitute the standard six-month regimen for drug-susceptible TB [54]. Though treating drug-resistant TB is much more complex, requiring the utilization of newer therapeutics and carefully designed combinations and regimens [55]. Multidrug-resistant TB (MDR-TB) is defined by resistance to isoniazid and rifampicin, and its treatment typically includes four of the five newest therapeutics: bed aquiline, pretomanid, linezolid, and moxifloxacin, depending on fluoroquinolone susceptibility, administered over six months [56]. Pre-extensively drug-resistant TB (pre-XDR TB), which is MDR-TB with additional resistance to any fluoroquinolone, poses an even greater treatment challenge. The emergence of extensively drug-resistant TB (XDR-TB), which includes resistance to bed aquiline and linezolid, is particularly concerning. This development forces a return to longer, potentially less effective treatments lasting 18-20 months [56]. The progression from MDR-TB to XDR-TB highlights the urgent need for continuous adaptation and innovation in TB treatment strategies.

Distinct from many other bacteria that are able to adopt resistance through horizontal gene transfer, *M. tuberculosis* relies solely on chromosomal mutations [57]. Resistance predominantly manifests through one of four mechanisms: modulation of efflux pumps, impairment of drug activity/activation, alteration of drug binding sites, or increase in target gene expression. Resistance to a single drug can arise via any of these primary pathways, as demonstrated by isoniazid, which can be resisted through each of the four. Starting with the process of cellular uptake, efflux pumps serve as key mediators in the regulation of intracellular drug concentrations. In a comprehensive review by Laws et al., over 30 distinct efflux pumps have been implicated in TB resistance, largely due to promoter mutations causing overexpression [58]. An example of particular concern is the upregulation of the *MmpL5* pump, which not only results in resistance to clofazimine but also displays cross-resistance to bedaquiline [59]. Many TB drugs are linked to multiple efflux pumps in their resistance profiles, such as isoniazid being associated with up to 18 [58]. It is unclear whether these associations directly cause resistance or facilitate it through other mechanisms. In the absence of adequate efflux, cellular therapeutic retention can produce resistance through modulating drug efficacy, either by deactivation or impeding drug activation. Drug deactivation can be exemplified through the overexpression of the *eis* gene, which encodes an acetyltransferase that acetylates and inactivates kanamycin [60]. Alternatively, isoniazid requires enzymatic conversion for its efficacy, a process disrupted by loss-of-function mutations in the *katG* gene [61]. Finally, if the drug navigates these barriers and converts to or remains in its active form, the last line of defence for the bacterium resides at the drug's molecular target. For isoniazid, the targeted enzyme is *inhA*, which plays a critical role in the biosynthesis of mycolic acid in the cell wall [62]. Resistance-conferring mutations in the *inhA* gene have been documented in both coding and promoter regions; the former compromises isoniazid binding affinity, while the latter induces elevated levels of *InhA* expression, necessitating toxic drug concentrations for effective inhibition [63]. In clinical strains, these mutations have been observed to co-occur, leading to high isoniazid resistance and cross-resistance to ethionamide [64].

Arguably, TB is the target of one of the most diverse repertoires of clinically approved drugs; nonetheless, resistance has emerged to all of them. On average, resistance to individual TB drugs has been reported 2.9 years (σ: 3.5) post-deployment, compared to 2.0 years (σ: 1.5) for combination therapies. Not all combination therapies implemented since 1948 are addressed in this review, due to the sheer number of treatment combinations that have been assessed. Of the combination therapies analyzed, statistical analysis reveals no significant disparity in resistance emergence between mono- and combination therapies (Mann-Whitney U test, $P = 0.89$). Proactive measures have been in place since 1966, with the National Tuberculosis Association advocating for susceptibility

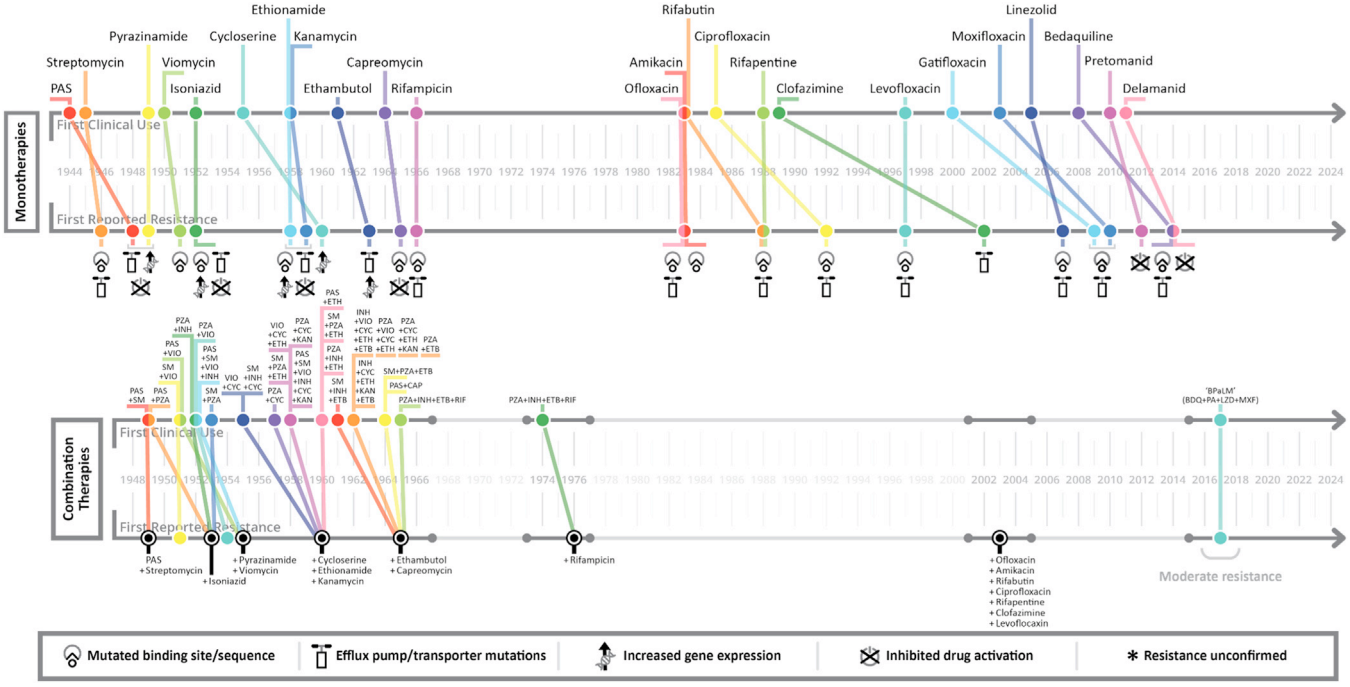

Fig. 3. Year of first clinical use and reported resistance for all deployed monotherapies and a selection of combination therapies for the treatment of *Mycobacterium tuberculosis* infection. Each individual-coloured line links the year either a monotherapy (upper) or combination therapy (lower) was first trialled on TB positive patients followed by the year resistance was first reported. The mechanism of action for each monotherapy (if known) has been indicated with one of four symbols: (Increased target gene expression), (Inhibition of drug activation), (Mutated binding site or sequence), and (Efflux pump mutations). Combination therapies have been abbreviated to enable better interpretation; para-aminosalicylic acid (PAS), streptomycin (SM), pyrazinamide (PZA), viomycin (VIO), isoniazid (INH), cycloserine (CYC), ethionamide (ETH), kanamycin (KAN), ethambutol (ETB), capreomycin (CAP), rifampicin (RIF), bedaquiline (BDQ), pretomanid (PA), linezolid (LZD) and moxifloxacin (MOX). Combinations have been represented by the largest combination trialled in that year (e.g. in 1952 PAS+INH, SM+INH, PAS+SM+INH, PAS+SM+VIO, PAS+SM+INH, SM+VIO+ETH, VIO+ETH and SM+VIO+INH are encompassed by the combination PAS+SM+VIO+INH) and year of resistance is displayed as the year a strain containing resistance towards all drugs in the largest combination was reported. The bordered black dots are the accumulation of new strains containing the listed resistances are all those previous.

testing and the use of at least two effective therapeutics in combination [65]. Unfortunately, the utilization of monotherapies continued and eventually led to resistance emergence and the proliferation of MDR-TB strains and the progression to XDR-TB. While completely antibiotic-resistant TB infections remain relatively rare, cases of untreatable infections have been documented. For example, a 2012 case involved a 39-year-old Tibetan refugee in India, who exhibited resistance to nine different TB therapeutics [66]. This patient remained on differing combinations of TB therapeutics for an extensive 38 months before obtaining a negative culture, which reverted to positive a mere two months after discontinuing the drug regime [66]. This case occurred prior to the approval and deployment of the newest antitubercular compounds bedaquiline and delamanid. Though the efficacy of delamanid and bedaquiline for this patient remains unreported, the absence of these advanced therapeutics could have led to, and may still result in, complete treatment failure. This shrinking 'cat and mouse' gap between drug discovery and the emergence of resistance, akin to patterns observed in HIV, underscores the pressing need for not just novel drugs and their swift implementation, but also for innovative strategies capable of circumventing the onset of resistance.

3.3. Protozoal infections

Unlike their viral and bacterial counterparts, protozoan pathogens present challenges rooted in their eukaryotic nature. The biochemical and metabolic resemblance between protozoa and human cells constrains the range of effective drug targets [67]. Moreover, parasitic protozoa have co-evolved with their hosts over millions of years, acquiring sophisticated immune evasion mechanisms that limit the utility of cytostatic treatments commonly used against bacteria [67,68]. The combination of these factors, and the fact that affected populations often reside in resource-poor settings, has culminated in a severely limited diversity of drug targets. In this constrained landscape, protozoan pathogens resort to familiar resistance mechanisms such as drug efflux systems and mutations that affect drug-binding sites, mirroring those seen in bacterial and viral pathogens. In the following section, we will explore these considerations in greater depth, focusing particularly on the challenges of drug resistance in malaria.

3.4. The historic build-up of malaria therapeutics and resistance

Malaria, a disease with a deep-rooted history, is speculated to have co-evolved with our pre-human ancestors over the course of 100 million years; early documentation of symptoms remarkably similar to those of malaria trace back to 2700 BC [69]. Despite major advancements in healthcare and the development of a wide array of therapeutic options, this disease continues to present a significant global health challenge, accounting for an estimated 249 million cases and 608,000 fatalities in 2022 alone [70]. The struggle against malaria has seen a long history of reliance on natural remedies. Historical records dating to 168 BC and pre-17th century folklore document the therapeutic use of *Artemisia annua* and the bark of the cinchona tree, deriving artemisinin and quinine, respectively [71,72]. These natural sources have served as the foundation for many of the antimalarial agents we use today. Given the long-standing application of these compounds, it is both expected and worrisome that their efficacy is dwindling due to the emergence of drug resistance, not only in *P. falciparum* but also in other *Plasmodium* species infecting humans (e.g. *P. vivax* and *P. malariae*). A complete timeline and breakdown of the modern use of mono- and

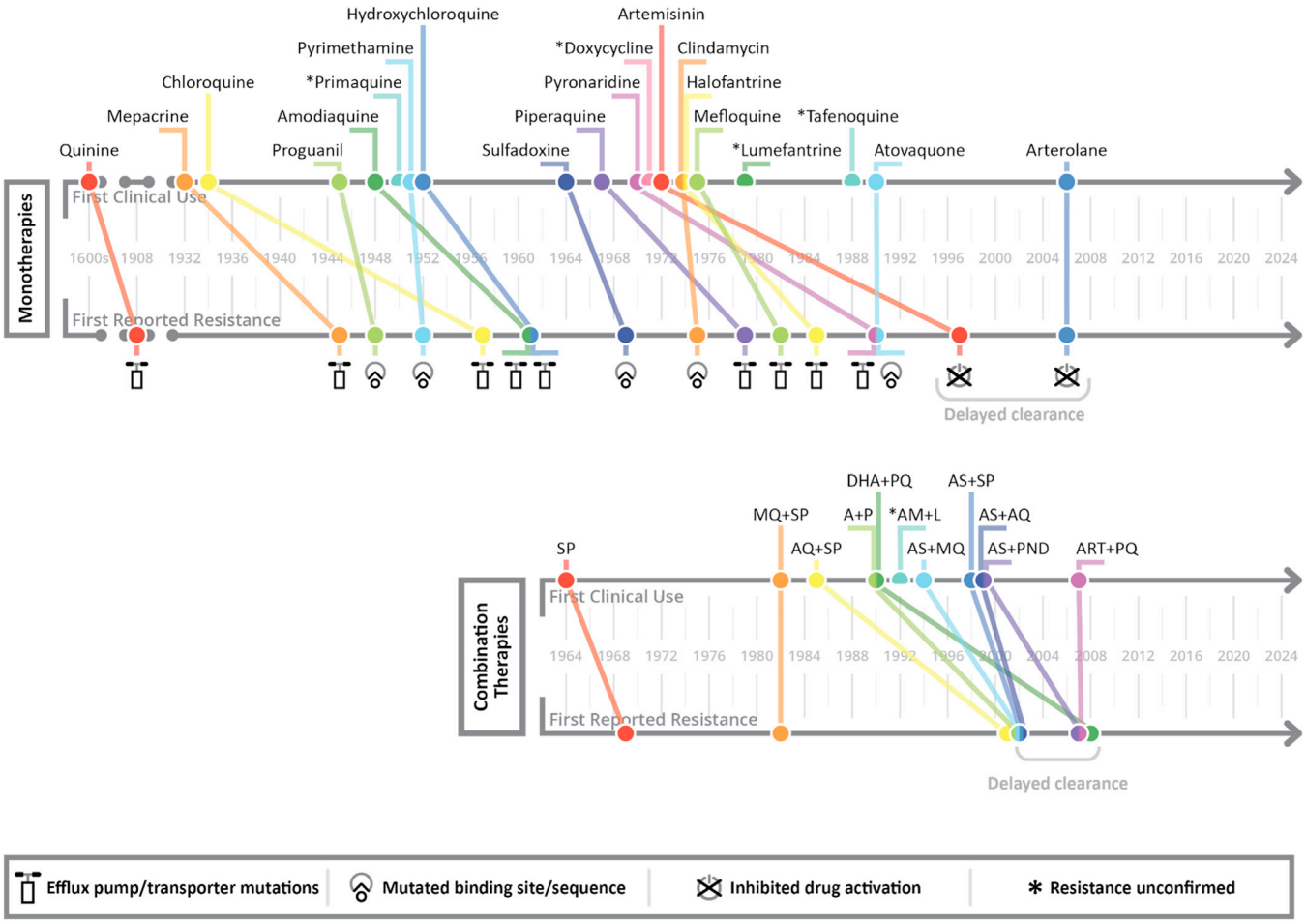

Fig. 4. Year of first clinical use and reported resistance for all deployed monotherapies and combination therapies for the treatment of malaria. Each individual-coloured line links the year either a monotherapy (upper) or combination therapy (lower) was first trialled on patients infected with the malaria causing parasites, followed by the year resistance was first reported. The mechanism of action for each monotherapy (if known) has been indicated with one of four symbols: (Increased gene expression), (Therapeutic inhibition), (Mutated binding site or sequence), and (Efflux pump mutations). Combination therapies have been abbreviated to enable better interpretation; sulfadoxine (SDX), pyrimethamine (PYR), artesunate (ATS), mefloquine (MFQ), atovaquone (ATO), proguanil (PG), artemether (ATM), lumefantrine (LUM), amodiaquine (ADQ), pyronaridine (PYN), dihydrogen-artemisinin (DHA), piperaquine (PPQ). Monotherapies and combinations without confirmed resistance are marked with an asterisk (*).

combination therapies since the 1600s employed against malaria can be seen in Fig. 4; for the compiled data on anti-malarial drugs and drug combinations, see Supplementary Table 5 & 6.

The majority of deployed antimalarial therapeutics belong to the aryl amino alcohol drug class, which shares a structural similarity with quinine and acts during the erythrocytic cycle of *Plasmodium* infection (see Fig. 5 for an overview of the *P. falciparum* life cycle). During this cycle, parasites convert toxic heme, a byproduct of haemoglobin digestion, into non-toxic hemozoin crystals. Most aryl amino alcohols (excluding 8-aminoquinolines) are believed to hinder this conversion process, and therefore to cause a heme build-up that results in parasite death [73]. Resistance to these therapeutics has developed through several genes that encode transporter pumps within the *P. falciparum* parasite (*Pfmdr1, Pfcrt, Pfmrp* and *Pfnhe1*), thus decreasing drug concentration at the target site [74]. In contrast, drugs such as atovaquone (a ubiquinone analog) and pyrimethamine (an antifolate) operate by directly binding and inhibiting their target molecules: ubiquinol, essential for the electron transport chain, and dihydrofolate reductase, required for amino acid synthesis [75]. In these cases, resistance is more straightforward, often only requiring a single point mutation in or around the drug binding site [75]. Artemisinin is more unique in its mechanism of action and resistance, with 'resistance', thus far, manifesting as a delayed parasite clearance time rather than complete resistance. Recent studies suggest that artemisinin and its derivatives are activated by degraded haemoglobin, exerting their antiparasitic effects through the accumulation of ubiquitinated proteins and translation repression [76,77]. The observed 'reduced clearance' phenotype has been associated with polymorphisms in the *Pfkelch13* propeller protein that is used for haemoglobin uptake [78]. Evidence suggests that inactivation of this gene reduces this uptake from the food vacuole that in turn triggers a dormant state of early erythrocytic stage parasites [77,79]. This dormancy subsequently decreases overall haemoglobin degradation that is required for artemisinin bioconversion, thereby contributing to delayed infection clearance [77].

Considering only the recent history of malaria treatments, resistance to monotherapies emerged after an average of 9.5 years (σ: 8.3), while combination therapies displayed resistance after a shorter average duration of 7.4 years (σ: 6.3). Mirroring trends observed in HIV and TB, in malaria, the timeframe before resistance develops does not show a statistically significant difference between monotherapy and combination therapies (Mann-Whitney U test, $P = 0.58$). This observation further emphasizes the detrimental consequences of deploying drug combinations in regions already exhibiting resistance to monotherapies. The use of artemisinin across the Greater Mekong Subregion provides a prime example of this, leading to the evolution of partially resis-

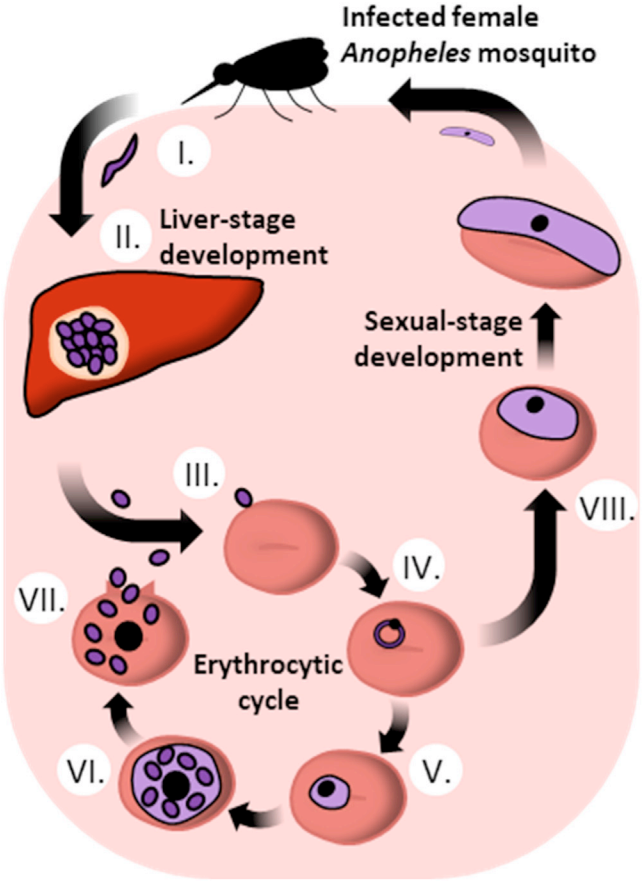

Fig. 5. *Plasmodium falciparum* life cycle. Injection of sporozoites into human bloodstream during female Anopheles mosquito blood meal (I). These sporozoites passively migrate through the bloodstream to the liver where they infect hepatocytes and undergo liver-stage development (II). Merozoites are released back into the bloodstream to infect erythrocytes (III). After entering the human host erythrocytes, the parasites form a ring-like structure (IV) before development into trophozoites (V) and finally schizonts (VI). Once developed, the cell ruptures allowing the schizont to release daughter merozoites (VII). After a single erythrocytic cycle, some parasites will undergo gametocytogenesis appearing initially as ring-stage parasites (IV). These parasites will then undergo the sexual-stage development (VIII) to then be ingested by a mosquito during a blood meal. Within the mosquito these gametocytes will develop into sporozoites to be injected back into the human host (adapted from Adderley *et. al*, 2020. [107])

tant parasites that exhibited the reduced clearance phenotype [80]. This clinical observation first occurred in 1997, a full nine years before the WHO guidelines advocated for the implementation of artemisinin combination therapies (ACTs) [81]. Subsequently, the implementation of ACTs in these regions soon revealed compromised efficacy with high levels of treatment failure [82]. The delay in parasite clearance by artemisinin resulted in higher parasite burdens on the partner drug, facilitating rapid resistance emergence. In response, intensive coordinated efforts were required to contain and manage these multi-drug resistant parasites [82]. However, recent reports from four regions across Africa have independently shown the emergence of artemisinin partial resistant parasites, once again raising concerns for malaria control efforts [70].

Despite the setbacks associated with artemisinin, there are glimmers of hope in the malaria landscape. Compounds like primaquine, tafenoquine, and lumefantrine offer potential avenues for treatment, although they too come with their distinct challenges. Primaquine and tafenoquine, as 8-aminoquinline pro-drugs, uniquely target the liver stage of infection and the transmission-essential gametocytes produced during the erythrocytic stages (see Fig. 5) [83]. The conversion of these pro-drugs into their active forms involves the human cytochrome P450 isozyme 2D6 (CYP2D6) enzyme [84]. As the host's genetic make-up controls the activator of these therapeutics, there is evidence that cases of documented 'resistance' might be better explained as treatment failure due to polymorphisms within the human CYP2D6 gene [85]. A significant drawback to the broader application of primaquine and tafenoquine is their potential to cause severe toxicity in patients with inherited glucose-6-phosphate dehydrogenase deficiency. This condition is prevalent in up to 30% of the population in certain malaria endemic regions [84]. Lumefantrine distinguishes itself among antimalarial drugs, having never been routinely used as a monotherapy since its introduction in 1979 [86]. To date, it has largely avoided significant resistance issues, maintaining efficacy even as some strains exhibit reduced susceptibility [87]. This antimalarial's pharmacokinetics require co-administration with a fatty meal for effective absorption, which poses challenges in regions with limited resources [88]. The ongoing efficacy of lumefantrine is vital for current malaria management strategies, heavily reliant on artemisinin-based therapies, particularly in areas where primaquine and tafenoquine are less tolerated. While no complete resistance has yet been documented, the evolving dynamics of malaria resistance underscore the need for continued vigilance.

4. Comparing drug resistance of HIV, TB, and malaria

The journey towards resistance for HIV, TB, and malaria treatments reveals intriguing patterns, particularly when comparing monotherapies across these diseases. As discussed in each individual section, a common feature across these infections is the implementation of combination therapies, typically following widespread resistance to each component used in isolation. Interestingly, when comparing the rate at which monotherapy resistance emerges, HIV and TB do not show a significant difference in the timeline for the development of resistance (Dunn's multiple comparisons test, $P > 0.99$) (Fig. 6). However, both these diseases display a more rapid emergence of resistance when compared to malaria, with both differences reaching statistical significance (Dunn's multiple comparisons test, $P = 0.01$ and $P = 0.02$, respectively). This result is somewhat counter-intuitive when considering the relative genomic complexity of the organisms: malaria, caused by six species of eukaryotic parasites, possessing larger and more complex genomes (23Mbp) than the viral HIV or bacterial TB (4.4Mbp); indeed, one might expect that such genomic complexity might enable the parasite to adapt a variety of ways to dispose of drugs, and thus that the resistance should be faster to emerge than for less complex organisms such as viral or bacterial pathogens. Some of the antimalarial drugs that elicited a slow or very slow resistance response, such as quinine, chloroquine and artemisinin derivatives, exert their effect not through a single molecular target, but through chemically-driven mechanisms (inhibition of heme polymerisation for quinine and chloroquine, generation of oxygen radicals for artemisinin), which prevents the selection of resistant genotypes based on a single mutation in the drug target; this may explain that resistance took longer to emerge against these compounds than against "classical" drugs that act by inhibiting specific enzymes (such as pyrimethamine of atovaquone, both of which showed rapidly selected resistance-conferring mutations in the target enzymes). Along a similar line of thought, one might expect the rate of resistance development to be slower for TB than for HIV, due to genomic complexity, replication rates, absence of proofreading activity in the HIV reverse transcriptase, and number of progeny genomes produced in an infected host; yet both appear to develop resistance at similar rates. This discrepancy may be due to the prevalence of cross-resistance and to the multi-mechanism resistance pathways available to *M. tuberculosis*. The mutational complexity of different pathways of resistance

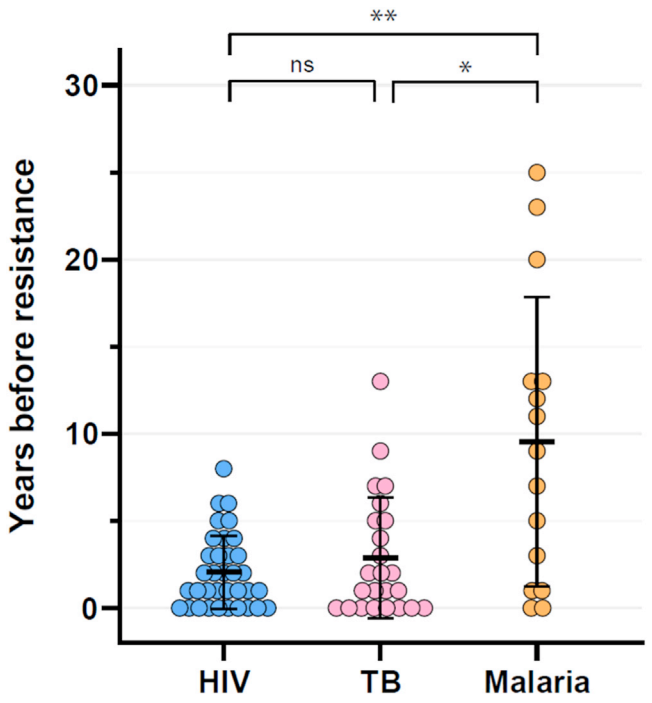

Fig. 6. Comparison of the number of years elapsed between the initial deployment of drugs against HIV, TB, and malaria and the first reports of resistance This plot represents the number of years before resistance was first reported to each monotherapy compound used in the treatment of HIV, TB, and Malaria. The means and standard deviations for each monotherapy is shown as black lines and significance as asterisks or ns (not statistically significance). HIV and TB show no significant difference ($p > 0.05$) in number of years for resistance to emerge towards a therapeutic compound following initial trial, whereas malaria resistance takes a significantly longer number of years compared to both HIV and TB ($p < 0.05$).

also impacts the timing of resistance emergence. This is particularly evident towards malaria treatments, where drugs necessitating more complex efflux mutations take an average of 13.5 years to develop resistance, while those involving simpler binding site mutations only require around 2.0 years (Mann-Whitney U test, $p < 0.01$). Other considerations relevant to this analysis are the differences in time between initial drug trialling and the extent of drug deployment. For instance, as malaria has a larger impact on the socioeconomically less developed nations, the deployment of new compounds is slower and less rapidly widespread than is the case for drugs against HIV, which is prevalent not only in low-income regions, but also in more affluent countries. While additional factors undoubtedly contribute to the variation in time till resistance for these pathogens, ranging from their diverse historical and geographical origins to various treatment deployment dynamics, one thing remains abundantly clear: resistance is an enormous and urgent challenge. The pressing need for innovative and alternative therapeutic solutions cannot be overstated.

5. Novel therapeutic approaches to combat AMR

In response to the growing threat of antimicrobial resistance, research efforts are increasingly focused on developing alternative therapeutic strategies. These approaches encompass; (1) enhancing existing antimicrobials, (2) creating novel compounds for precise pathogen or pathogen gene targeting, and (3) adopting innovative approaches that target host factors. Nanotechnology is emerging as a transformative tool to augment the effectiveness of antimicrobials, promising to improve drug bioavailability, optimize drug accumulation in microbial hiding places, and minimize drug-related toxicities that can hinder patient adherence, thus curbing the emergence of drug resistance. This potential is particularly promising in the case of persistent challenges such as malaria, tuberculosis, and HIV. The utilization of nano-sized carriers for drug delivery and vaccine formulation opens new avenues to overcome traditional treatment constraints. This potential has been extensively reviewed, particularly focusing on HIV, TB, and malaria, by Kirtane et al. [89]. In tandem with these advancements, innovative compounds with selective pathogen-targeting mechanisms are under rigorous investigation. These include antimicrobial peptides, monoclonal antibodies, CRISPR-Cas gene editing, and microbiota transplants [90]. Diverging from traditional approaches, host-directed therapies (HDT) offer an innovative strategy by targeting host factors to impede pathogen resistance, as the fastet path to resistance (mutation in the drug target) is not available to the pathogen because the target is not under its genetic control [91]. Some of these compounds have already found application in disease treatment. For example, the approved HIV-1 entry inhibitor, maraviroc, effectively targets a protein on the surface of white blood cells that the virus exploits for entry, thereby blocking infection [92]. Notably, kinase inhibitors have garnered significant scholarly attention for their potential in drug repurposing and the treatment of diverse diseases [93].

6. Concluding remarks

In summary, this review underscores the urgency and complexity of addressing antimicrobial resistance in the persistent challenges of HIV, TB, and malaria. While significant strides have been made in understanding the mechanisms of resistance across these diseases, it is clear that the emergence of resistance is a multifaceted phenomenon influenced by host genetics, the mutational complexity of the pathogens, and the pharmacodynamics of the therapeutic agents. Here we highlighted that, across these diseases, the timelines for the emergence of resistance are alarmingly short, urging an immediate need for innovative therapeutic strategies. Combination therapies, adopted for all three diseases, mitigated the resistance problem without fully solving it; pre-existing resistance to any single drug used in the combination facilitated the emergence of resistance to the combined therapies. This calls for an absolute avoidance of using any new drugs in single therapy configuration. Emerging technologies, such as nanocarriers for drug delivery and CRISPR-Cas gene editing, offer promising avenues for future research and potential clinical interventions. Host-directed therapies, which focus on modifying the host's interaction with the pathogen rather than targeting the pathogen itself, also present an potentially powerful alternative for mitigating resistance. As we move forward, it is imperative to focus on the development and strategic deployment of new drugs, as well as the optimization of existing therapies, to forestall the devastating impact of antimicrobial resistance. Continuous vigilance, interdisciplinary collaboration, and global commitment are essential for mounting an effective response to this looming crisis.

7. Methods

7.1. Literature search strategy

The literature search was performed to identify the earliest reports of therapeutic use and resistance emergence for monotherapy drugs targeting HIV, TB, and malaria. Initial scholarly searches were conducted using the specific therapeutic drug name alongside the corresponding pathogen name (e.g., "Chloroquine malaria"). The search strategy involved narrowing down the publication dates progressively backward in annual increments from the earliest apparent year until no relevant articles were identified. Subsequently,

searches proceeded forward yearly until the first documented human clinical trial or case report was located.

When a drug was known by a previous or alternative compound name, this earlier designation was employed in the search. The year identified was further refined based on details provided within the articles:

1. If the exact year of trial initiation or resistance emergence was explicitly stated within the article, this year was adopted.
2. If only the duration of the trial was specified (e.g., 12 months), this duration was subtracted from the article's submission year to estimate the year of trial initiation.
3. If neither the specific year nor trial duration was provided, the article submission year was taken as the reference.

To identify the emergence of resistance, additional searches incorporated terms such as "resistance," "resistant," "tolerance," "clinical failure," "failure," or "treatment failure" alongside drug names or previous compound names. Similar backward and forward annual searching was performed to pinpoint the earliest documented case of resistance.

Combination therapies for HIV and malaria were identified from FDA-approved and licensed combinations, with literature searches performed using each constituent drug name following the methodology described above. For TB, established combinations were less defined; therefore, searches were executed using specific therapeutic drug names in conjunction with the keyword "combination," or identified via documented case studies and clinical trials. Resistance to TB combination therapies was initially assessed through searches identifying resistance directly attributed to specific combinations, and subsequently expanded to locate susceptibility studies. The earliest documented occurrence of resistance in clinical isolates or patients against all drugs within a given combination was recorded as the year resistance was first reported.

7.2. Statistical analysis

Statistical analyses were conducted using GraphPad Prism software version 10.3.1. Comparisons between monotherapy and combination therapy groups for each pathogen (HIV, TB, malaria) were performed using the Mann-Whitney U test, a non-parametric test that does not assume a normal distribution of data.

Sample sizes for each group analyzed were as follows:

- HIV: monotherapies (n = 35), combinations (n = 18).
- TB: monotherapies (n = 24), combinations (n = 36).
- Malaria: monotherapies (n = 15), combinations (n = 10).

No additional assumptions were made beyond the standard assumptions inherent in using the Mann-Whitney U test, specifically that observations are independent and the data are continuous in nature.

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Declaration of competing interests: None declared.

Ethical approval: Not required.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jgar.2025.07.014.

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