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REVIEW ARTICLE

Epidemiology, Clinical Manifestations, and Outcome of Mucormycosis in Solid Organ Transplant Recipients: A Systematic Review of Reported Cases

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Mucormycosis is an emerging disease primarily affecting the immunocompromised host, but scarce evidence is available for solid organ transplant recipients (SOTRs). We systematically reviewed 183 cases occurring in SOTRs, exploring epidemiology, clinical characteristics, causative pathogens, therapeutic approaches, and outcomes. Kidney transplants accounted for half of the cases, followed by heart (18.6%), liver (16.9%), and lung (10.4%). Diagnosis showed a dichotomous distribution, with 63.7% of cases reported within 100 days of transplantation and 20.6% occurring at least 1 year after transplant. The 90-day and 1-year mortality rates were 36.3% and 63.4%, respectively. Disseminated disease had the highest mortality at both time points (75% and 93%). Treatment with >3 immunosuppressive drugs showed a significant impact on 90-day mortality (odds ratio [OR], 2.33; 95% CI, 1.02–5.66; $P = .0493$), as did a disseminated disease manifestation (OR, 8.23; 95% CI, 2.20–36.71; $P = .0027$) and the presence of diabetes (OR, 2.35; 95% CI, 1.01–5.65; $P = .0497$). Notably, prophylaxis was administered to 12 cases with amphotericin B. Further investigations are needed to validate these findings and to evaluate the potential implementation of prophylactic regimens in SOTRs at high risk.

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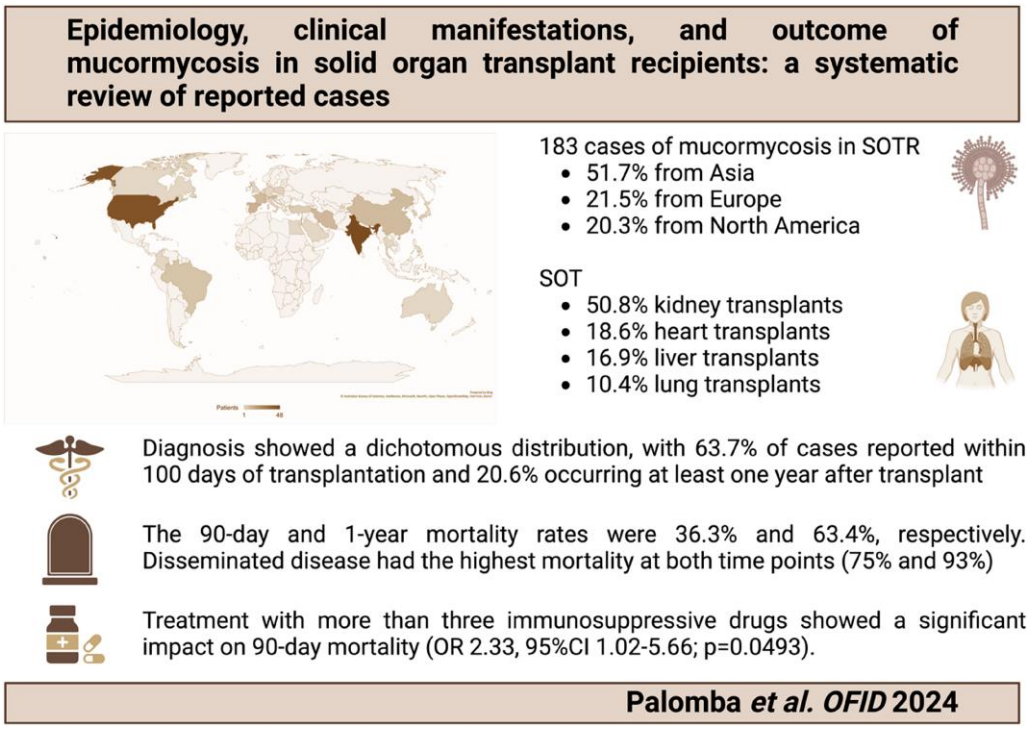
Graphical Abstract



Keywords. epidemiology; mortality; mucormycosis; organ transplant; systematic review.

INTRODUCTION

In recent years, the global burden of invasive fungal disease caused by pathogens from the order Mucorales—including *Rhizopus*, *Rhizomucor*, *Mucor*, *Lichtheimia*, *Apophysomyces*, *Cunninghamella*, *Saksenaea*, and other rarer species [1]—has grown to become the second-most common pathogens after *Aspergillus* in patients with hematologic malignancies, hematopoietic stem cell transplantation, and solid organ transplantation (SOT) [2, 3]. Mucorales primarily infects humans when spores are inhaled, with the lungs and sinuses being common sites of initial infection. Additionally, infections can occur through skin breaks, burns, or traumatic injuries involving soft tissues.

Invasive mucormycosis predominantly affects individuals with compromised immune systems (eg, uncontrolled diabetes mellitus) and significant comorbidities, especially when risk factors are present, such as trauma or indwelling of medical devices. In immunocompromised hosts, the initial colonization can lead to severe conditions, spreading to the eyes, central nervous system, and gastrointestinal tract. Mucormycosis is a severe condition, with mortality rates ranging from 46% to >90%, depending on disease localization, patients' immune status, and species identified [1, 4]. The main therapeutic option is surgical debridement, supported by antifungal treatment. Antimicrobial resistance is difficult to define, as clinical breakpoints have not been established [5]. The diagnosis of mucormycosis is often complicated, and recent advances in mycology have shown that the burden of the disease is more significant than expected a few decades ago [6]. In addition, progress in transplantation medicine and oncohematology, along with the diffusion of immunomodulating therapy for patients with other diseases (eg, autoimmune conditions), has undoubtedly widened the population at risk of invasive fungal disease.

The limited evidence on mucormycosis is currently derived from clinical studies, predominantly case reports and case series. This is especially evident for individuals who have undergone SOT. Therefore, we performed a systematic review of cases of mucormycosis in SOT recipients (SOTRs) published between January 2002 and December 2022. We aimed to explore the epidemiology, clinical and radiologic characteristics, causative pathogens, therapeutic approaches, and outcomes within this specific population.

METHODS

The study protocol of this systematic review was registered on PROSPERO (CRD42023387356) and reported following the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-analyses) [7]. The electronic search was performed on the PubMed, Scopus, and Embase databases with

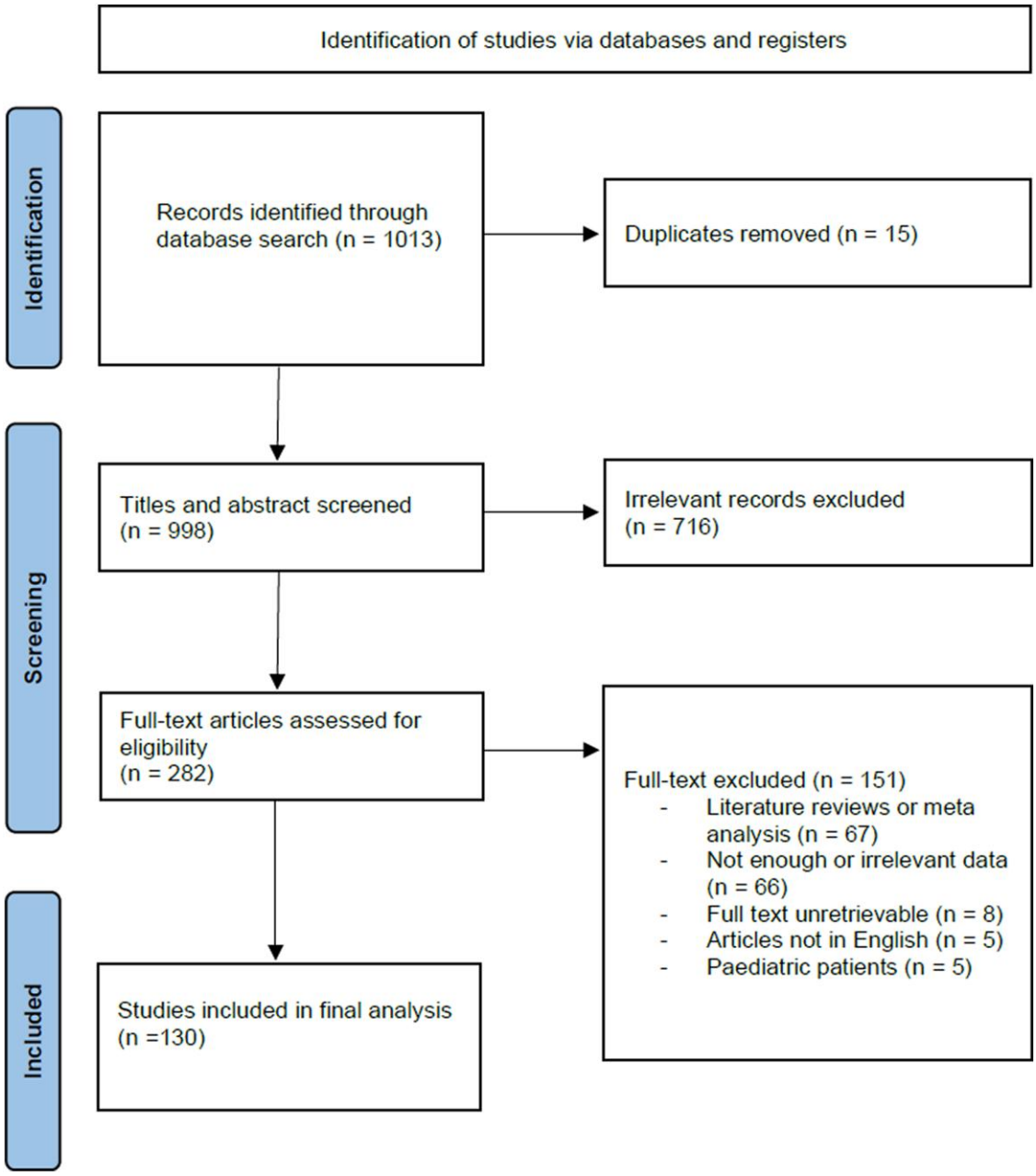


Figure 1. PRISMA diagram depicting the case selection process. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

keywords referring to mucormycosis and SOT. Searches were limited to studies involving humans and those published in English from January 2002 to December 2022. A manual search of publications that the electronic search might have missed was subsequently performed. The details of this search are presented in the Supplementary Table 1.

Eligibility Criteria

We reviewed the published case reports and case series of proven/probable mucormycosis [8, 9] occurring in adult patients who have undergone SOT. Studies had to describe a case of mucormycosis occurring in adult SOTRs; we did not apply exclusion criteria regarding the availability of all the selected study variables. Studies were excluded if (1) they were congress abstracts, letters, or commentaries; (2) they included only patients aged <18 years; and (3) they computed mortality excluding early deaths. Mortality was considered at 2 time points: 90 days and 1 year after mucormycosis diagnosis.

Screening of the Articles and Data Extraction

The records identified through the electronic search were exported to a specifically developed electronic spreadsheet. Four

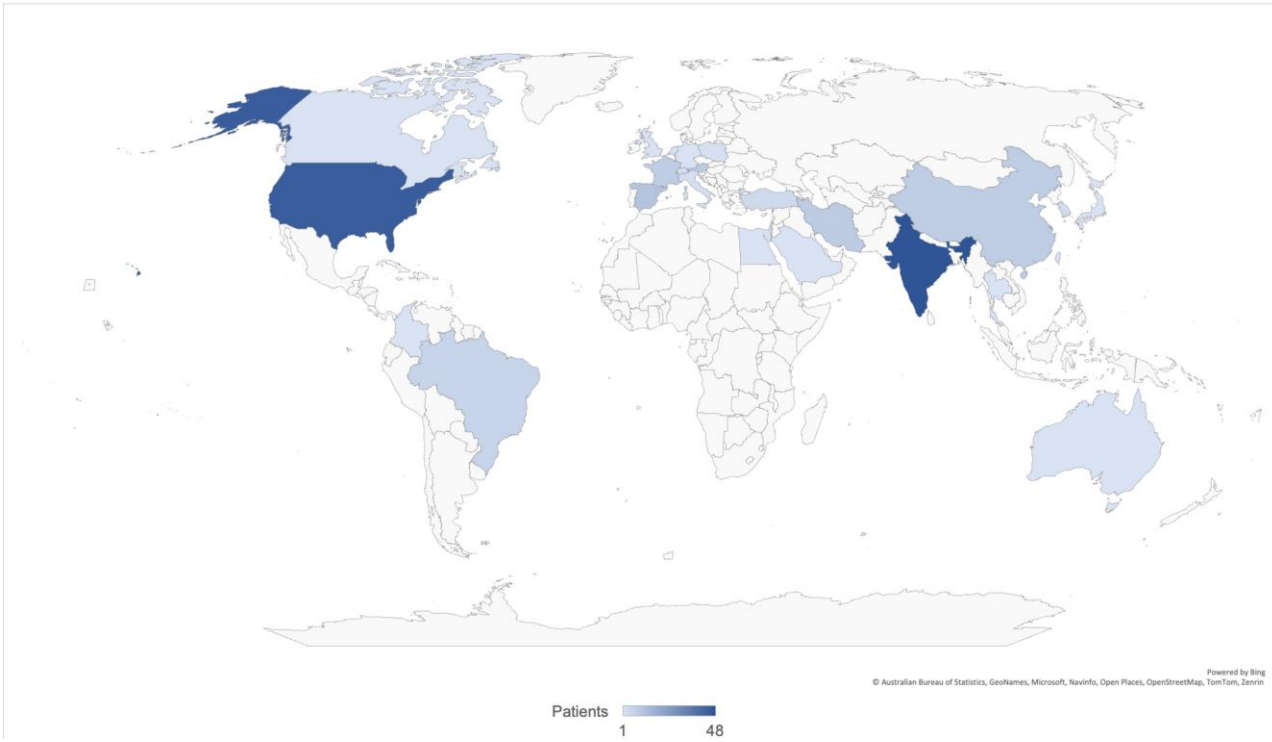


Figure 2. Geographic distributions of mucormycosis cases in solid organ transplant recipients in our review. The higher the color intensity, the higher the number of patients from the country.

authors independently screened the titles and abstracts of the records, assessing them against predefined criteria for inclusion and exclusion. Following this initial screening, the full texts of the selected documents were obtained and scrutinized against the same criteria. Consensus discussions involving a fifth reviewer resolved any discrepancies during these 2 phases.

Four independent reviewers performed the data extraction, and disagreements regarding the inclusion of studies were resolved through consensus. In cases where we encountered missing data within a considered article, we reached out to the authors to request undisclosed information or additional details. Extracted variables were as follows:

- Characteristics of the studies: author and title, country, publication year, study design, and number of patients
- Sociodemographic characteristics of the patients in the studies: age, sex, and ethnicity
- Clinical characteristics of the patients in the studies, including underlying conditions at the time of infection: diabetes mellitus, renal replacement therapy, major trauma, cytomegalovirus disease, liver disease or malignancies after SOT, neutropenia, and iron overload
- SOT characteristics of the patients in the studies: SOT type (kidney, heart, liver, lung, or other solid organs), time since SOT, SOT-related complications, and SOT-related treatments—namely, number and type of administered immunosuppressant drugs and prophylactic antifungal therapies
- Characteristics of the mucormycosis infection affecting the patients in the study: the identified microorganism, the disease's manifestations, the chest image results, and the type of administered therapeutic antifungal agents. Specifically, we categorized the clinical manifestations of mucormycosis, which can involve rhino-orbital cerebral, pulmonary, cutaneous, or disseminated forms, according to the primarily affected body sites and the extent of infection at the point of diagnosis. We applied criteria adapted from previous definitions for this categorization [1].
- Data about the need for surgery, retransplantation, 90-day and 1-year mortality, and surgical sequelae

Study Outcomes

The study's primary outcome was to describe clinical and microbiologic characteristics of SOTRs who developed mucormycosis. The secondary aim was to assess those demographic and clinical characteristics associated with 90-day mortality of SOTRs who developed mucormycosis.

Statistical Analysis

Study characteristics were described by count and percentage or median and IQR, as appropriate. A descriptive summary

Table 1. Epidemiologic and Clinical Characteristics of SOT Recipients With Mucormycosis

Variable	No. (%)[a]
Sex	183
Male	136 (74.3)
Female	47 (25.7)
Age, y, median (IQR)	40.0 (40–56.5)
Underlying condition at time of infection	
Diabetes mellitus	73/173 (42.2)
Renal replacement therapy	30/137 (21.9)
Major trauma[b]	18/183 (9.8)
Cytomegalovirus disease	10/183 (6.0)
Liver disease after SOT	10/137 (7.3)
White blood cell count, <500/mm^3	3/183 (1.6)
Iron overload	2/165 (1.2)
Malignancies after SOT	2/137 (1.5)
SOT type	183
Kidney	93 (50.8)
Heart	34 (18.6)
Liver	31 (16.9)
Lung	19 (10.4)
Other[c]	6 (3.3)
Time since SOT	165
<30 d	58 (35.2)
30–100 d	47 (28.5)
101–180 d	11 (6.7)
181–365 d	15 (9.1)
>1 y	34 (20.6)
SOT complications	
Rejection	46/149 (30.9)
Reoperation	27/178 (15.2)
Re-transplantation	18/178 (10.1)
No. of immunosuppressants	183
≤3	52 (28.4)
>3	131 (71.6)
Antifungal prophylaxis	164
No	108 (65.9)
Yes	56 (34.1)
Antifungal agent used for prophylaxis[d]	53
Fluconazole	20 (37.8)
Amphotericin B	12 (22.6)
Terbinafine	6 (11.3)
Voriconazole	4 (7.5)
Anidulafungin	3 (5.7)
Flucytosine	3 (5.7)
Nystatin	3 (5.7)
Micafungin	2 (3.8)

Abbreviation: SOT, solid organ transplantation.

[a]Percentage of the available records.

[b]Motor vehicle accident, surgery, natural disaster, open wound.

[c]Other: 2 multivisceral transplantations (stomach, liver, duodenum-pancreas, small bowel, colon), 1 liver-pancreas, 1 liver-kidney, 1 kidney-heart, 1 kidney-pancreas.

[d]53 cases where antifungal agent used for prophylaxis was available.

Table 2. Microbiological, Clinical, and Therapeutic Characteristics of Mucormycosis Solid Organ Transplant Recipients

Variable	No. (%)[a]
Organism identified	124
Rhizopus spp	52 (41.9)
Mucor spp	35 (28.2)
Lichtheimia spp[b]	20 (16.1)
Cunninghamella spp	6 (4.8)
Rhizomucor spp	5 (4.0)
Apophysomyces spp	4 (3.2)
Saksenaea complex	1 (0.8)
Other, unspecified	1 (0.8)
Disease manifestation	171
Pulmonary	42 (24.6)
Rhino-orbital cerebral	42 (24.6)
Gastrointestinal	29 (17.0)
Cutaneous	27 (15.8)
Disseminated	17 (10.0)
Other[c]	14 (8.2)
Chest imaging	80
Lobular consolidation	28 (35.0)
Cavitary lesion	23 (28.8)
Disseminated	3 (3.8)
Solitary nodule	3 (3.8)
No lesion	2 (2.5)
Other	21 (26.2)
Antifungal agents administered	183
Amphotericin B	163 (89.1)
Posaconazole	49 (26.8)
Anidulafungin	4 (3.0)
Fluconazole	3 (1.6)
Isavuconazole	5 (2.7)
Ketoconazole	3 (1.6)
Micafungin	5 (2.7)
Nystatin	5 (2.7)
Voriconazole	9 (5.0)
Caspofungin	5 (2.7)
Itraconazole	2 (1.1)
Terbinafine	1 (0.5)

[a]Percentage of the available records.

[b]*Lichtheimia* spp, formerly *Absidia* spp.

[c]Other disease localizations: 5 renal infections, 3 hepatic infections, 1 oral infection, 1 endovascular device infection, 1 mediastinitis, 3 unspecified.

was performed for patient characteristics, disease symptoms, and the pathogens causing the disease. Categorial variables were evaluated by chi-square or Fisher exact test. A multivariate logistic regression to assess the risk factors associated with 90-day mortality of mucormycosis was then performed, adjusting for demographic and clinical features (age, sex, type of SOT, rejection, diabetes mellitus, disseminated disease, presence of surgical treatment and therapy with >3 immunosuppressive drugs). $P \leq .05$ indicated statistical significance. Analyses were performed with R version 4.2.1.

RESULTS

A total of 1013 articles were identified through the database search. After removal of duplicates and screening of titles and abstracts, 282 full-text articles were assessed for eligibility, with 130 studies in the final analysis: 117 case reports of single patients [10–125], 8 case reports of 2 patients [126–133], 4 case series describing ≥3 patients [134–137], and a multicenter

Table 3. Outcomes of 183 Solid Organ Transplant Recipients With Mucormycosis

Variable	Rhino-orbital Cerebral (n = 42)	Pulmonary (n = 42)	Cutaneous (n = 27)	Disseminated (n = 17)	Gastrointestinal (n = 29)	Other[a] (n = 14)	Total (N = 183)
Surgical intervention	25/42 (59.5)	16/39 (41.0)	14/27 (51.9)	3/17 (17.6)	18/29 (62.1)	11/14 (78.6)	88/179 (49.2)
90-d mortality	12/41 (29.3)	16/37 (43.2)	6/26 (23.1)	12/16 (75.0)	11/29 (37.9)	4/12 (33.3)	62/171 (36.3)
1-y mortality	12/20 (60.0)	18/26 (69.2)	10/15 (66.7)	14/15 (93.3)	12/22 (54.5)	4/12 (33.3)	71/112 (63.4)
Need for retransplant	0/18 (0.0)	2/23 (8.7)	0/14 (0.0)	1/14 (7.1)	2/20 (10.0)	1/12 (8.3)	6/102 (5.9)
Surgical sequelae	2/18 (11.1)	0/22 (0.0)	2/13 (15.4)	1/12 (8.3)	3/20 (15.0)	1/12 (8.3)	9/98 (9.2)

[a]Other disease localizations: 5 renal infections, 3 hepatic infections, 1 oral infection, 1 endovascular device infection, 1 mediastinitis, 3 unspecified.

observational study of 30 patients [138], accounting for a total of 183 cases of mucormycosis in SOTRs (Figure 1).

Demographic Characteristics and Underlying Conditions

The 183 patients with mucormycosis analyzed in our study were predominantly male (n = 136, 74.3%), and their median age was 40 years (IQR, 40–56.5). Half of cases (51.7%) were from Asia, while Europe and North America accounted for 21.5% and 20.3% of reports, respectively. The geographic distribution of cases is depicted in Figure 2. Diabetes mellitus was the most common underlying condition (73/173, 42.2%), followed by renal replacement therapy (30/137, 21.9%) and major trauma (18/183, 9.8%), while other conditions were infrequent, such as severe neutropenia (white blood cell count <500 cells/mm^3; 7.3%) and iron overload (6%). Patients' demographics and underlying conditions are described in Table 1.

SOT Characteristics

Half of the cases were represented by kidney transplant (KT) recipients (93/183, 50.8%), followed by heart (34/183, 18.6%), liver (31/183, 16.9%), and lung (19/183, 10.4%). Mucormycosis was diagnosed more frequently within the first 30 days post-SOT (58/165, 35%), and 63.7% of cases were reported within 100 days from transplantation. One-fifth of infections (34/165, 20.6%) were diagnosed after at least 1 year from transplant. The most frequent SOT complication described preceding mucormycosis was rejection (46/149, 30.9%), while one-fourth of patients underwent reoperation or retransplantation (45/178, 25.2%). Regarding the immunosuppressive drugs used, 71.6% (131/183) of patients received >3 drugs, with corticosteroids, tacrolimus, and mycophenolic acid being the most common. One-third of SOTRs (56/164, 34%) received antifungal prophylaxis, which was potentially effective against Mucorales (amphotericin B [AmB]) in 22.6% of cases (12/53; Table 1 and Supplementary Table 2).

Microbiological, Clinical, and Therapeutic Characteristics

Rhizopus was the most common species isolated from clinical specimens (52/124, 41.9%) and, with *Mucor* and *Lichtheimia*, accounted for 86.2% (107/124) of cases. The 2 most common disease manifestations were pulmonary and rhino-orbital cerebral, each with 24.6% of reports, while 10% of cases (17/171) were from disseminated disease. AmB was the most used antifungal agent (163/183, 89.1%) and was mainly administered as first-line intravenous therapy for a median 40 days. Posaconazole was given in a quarter of all cases (49/183, 26.8%) and was mainly used as oral step-down therapy for an average of 93 days after intravenous AmB. When antifungal susceptibility essays were available, AmB and posaconazole were active in less than a third of cases, at 31% (9/29) and 30% (9/30), respectively (Table 2, Supplementary Tables 3 and 4).

Outcomes by Disease Manifestation

Surgical debridement was performed in half of the cases (88/179, 49.2%), more frequently in gastrointestinal (18/29, 62.1%), rhino-orbital cerebral (25/42, 59.5%), and cutaneous (14/27, 51.9%) forms and less frequently in disseminated disease, which accounted for 17.6% (3/17) of cases. The overall 90-day and 1-year mortality rates were 36.3% (62/171) and 63.4% (71/112), respectively. Disseminated disease had the highest mortality at both time points, with 75% (12/16) of patients dying at 90 days and 93% (14/15) of patients not surviving at 1 year. When localized disease was analyzed, pulmonary (16/37, 43.2%) and gastrointestinal (11/29, 37.9%) involvement had the lowest survival rate at 3 months after disease onset, while cutaneous forms had the lowest mortality (6/26, 23%). Two-thirds of patients affected by any form had died in 1 year (Table 3).

Variables Associated With 90-Day Mortality

Regarding the secondary outcome, after accounting for potential confounders (age, sex, SOT type, rejection, diabetes mellitus, disseminated disease, presence of surgical treatment, and administration of >3 immunosuppressant drugs after SOT), the multivariate logistic regression model showed that the following had a significant impact on 90-day mortality: disseminated form (odds ratio [OR], 8.23; 95% CI, 2.20–36.71; $P = .0027$), diabetes mellitus (OR, 2.35; 95% CI, 1.01–5.65; $P = .0497$), and being treated with >3 immunosuppressant drugs (OR, 2.33; 95% CI, 1.02–5.66; $P = .0493$; Supplementary Table 5).

DISCUSSION

In this systematic review, we provided new insights into epidemiology, clinical and microbiological characteristics, management approaches, and outcomes of SOTRs affected by mucormycosis. Furthermore, our investigation confirmed the critical role of immunosuppression in supporting disease development and influencing mortality rates within this vulnerable cohort.

Half of the cases originated from Asian countries, while North America and Europe each contributed a fifth. This geographic distribution may be partly explained by the high prevalence of type 2 diabetes in Asia, a well-known risk factor for mucormycosis, particularly given that >60% of the world's patients with diabetes reside in this continent [139]. This factor likely compounds with other risk factors among SOTRs, emphasizing the highlighted geographic pattern. Moreover, countries undergoing rapid industrial and economic growth, such as China and India, face social and environmental issues that significantly contribute to fungal diseases. These issues, including air pollution, reduced biodiversity, and meteorological conditions, may elevate host exposure to pathogens [140]. Finally, it should be noted that a substantial portion (16%) of analyzed cases came from a large multicenter study in India [138], which undeniably influenced the overall geographic distribution of cases.

In line with previous studies [4], mucormycosis was reported more frequently in KT recipients, accounting for 51.8% of cases. This finding may be mainly attributed to the higher global prevalence of KT, which accounts for 64% of SOTs worldwide [141]. However, other factors may be at play. First, diabetic nephropathy, accounting for >40% of KT [142], persists as a significant risk factor posttransplant due to ongoing impaired glucose metabolism and showed a significant impact on 90-day mortality in our multivariate analysis. Second, KT candidates are frequently hyperimmunized due to previous exposure to foreign antigens, particularly human leukocyte antigens [143]. This poses a challenge because it increases the risk of hyperacute or acute antibody-mediated posttransplant rejection, requiring specific immunosuppressive regimens or strategies (eg, plasmapheresis) that may increase the global "net state of immunosuppression," resulting in an enhanced infectious risk [144]. Finally, up to 30% of people who receive a KT will experience some degree of rejection [145], which exposes the patient to higher levels of immunosuppression and increases the risk of graft loss and the need for retransplantation or additional surgical procedures. Overall, it appears that immunosuppression, both iatrogenic and related to the patient's underlying conditions, plays a pivotal role in driving the occurrence of mucormycosis.

Concerning the transplant procedure, the onset of mucormycosis exhibited a dichotomous distribution, with 63.7% of cases reported within 100 days of transplantation and 20.6% diagnosed at least 1 year after SOT. These findings differ from the paradigmatic infection timeline after SOT, which places the onset of invasive fungal disease at 6 to 12 months posttransplant [146]. The prolonged state of immunosuppression undoubtedly contributes to developing mucormycosis following SOT. Still, its onset appears to be influenced by the intensity rather than the duration of the impairment of the immune system. Indeed, the cases were characterized by a high prevalence of rejection (30%) and by the use of >3 immunosuppressive drugs (71.6%). The latter significantly affected 90-day mortality in the multivariate logistic regression model (OR, 2.33; 95% CI, 1.02–5.66; $P = .0493$).

Interestingly, we observed cases of infection in SOTRs even when antifungal prophylaxis was administered. While this observation is less relevant in instances where fluconazole or voriconazole was used, since these agents are usually ineffective against Mucorales, it is concerning to highlight that 12 cases were reported in patients receiving AmB, the first-line agent for mucormycosis in those without preexisting renal disease [147]. Unfortunately, it was impossible to verify the administration schedule or the dosage employed to understand the role of subtherapeutic drug concentration. Still, these data stress the concept of possible breakthrough mucormycosis despite ongoing prophylaxis with AmB, as reported for other invasive fungal infections, such as aspergillosis [148, 149]. Where noted, antimicrobial susceptibility testing (AST) showed a lack of activity for agents considered among the main treatment options for mucormycosis. Particularly, AmB was inactive against the isolate in 30 cases, while posaconazole, the first-line agent (with isavuconazole) for patients with renal impairment, was inactive in 21 cases. These results highlight the importance of obtaining the AST for the clinical management of patients with mucormycosis. They also support the use of combination therapy as a first-line approach in cases where AST is unavailable despite scarce evidence from available studies [150].

Consistently with previous reviews of cases [1, 4], *Rhizopus* and *Mucor* were the most prevalent species. The landscape of mucormycosis etiology will be shaped in the following decades by climate change and mycology advances. The latter will allow the detection of cases that would have been previously misdiagnosed or not identified. A recent study [6] identified a novel *Apophysomyces* species, highlighting the importance of collaboration among clinicians, pathologists, and microbiologists to achieve timely diagnosis using a combination of conventional culture, phenotypic, and morphologic analysis with molecular testing based on real-time polymerase chain reaction.

The spectrum of manifestations in SOTRs closely mirrors that in a recent systematic review involving 851 patients, irrespective of underlying conditions. Pulmonary and rhino-orbital cerebral manifestations accounted for half of the cases (49.2%), whereas disseminated disease was diagnosed in 10% of patients, as

compared with 54% and 13%, respectively, reported by Jeong et al. Interestingly, we found a higher incidence of gastrointestinal manifestations (17% vs 8%) [4]; this may be partially explained by the fact that abdominal surgery was performed in most cases. Notably, the disseminated form showed a significant association with 90-day mortality.

The predominant treatment approach involved combination therapy, with AmB as the backbone, followed by or with an azole (most commonly posaconazole). The duration of treatment exhibited heterogeneity, with initial intravenous therapy lasting a median 40 days, followed by oral step-down treatment for a median 3 months. The optimal duration for treating mucormycosis remains undefined and is often intricately linked with immunosuppression management. Recent literature suggests a mean duration of approximately 6 months [147], which is consistent with our findings. Shorter regimens in SOTRs are typically reserved for patients with relatively mild disease and those whose surgical debridement has successfully achieved source control.

Surgery was indeed performed in half of the patients (49.2%). Analysis of the different manifestations revealed that patients with gastrointestinal, rhino-orbital cerebral, and cutaneous forms underwent surgery more frequently (62.1, 59.5%, and 51.9%, respectively), while only 17.6% of those with disseminated disease were treated surgically. As stated by recent international guidelines, surgical treatment is the mainstay of mucormycosis management whenever viable, leading to higher cure and survival rates [147]. Surgery can be separated into major groups: debridement of the skin and soft tissue, debridement of rhino-orbital cerebral mucormycosis, orbital exenteration, lung resection, and debridement of bone, as well as visceral resections in, for example, liver, spleen, peritoneal structures, or transplanted organs. The surgical approach should be timely and complete, requiring repeated resection or debridement.

In our analysis of cases, mucormycosis mortality rates at 3 and 12 months were significant, as expected, particularly for pulmonary (43.2% and 69.2%) and disseminated (75% and 93.3%) forms. However, with 63.4% of patients dying in 1 year, the overall mortality rate for any manifestation of the disease was notable and higher than the 48% reported by Roden et al in the only available analysis that included details on SOTRs [1]. These findings may be partly explained by the predominance of cases from Asia, where the prognosis is worse, and by changes in the characteristics of patients undergoing transplantation over the last 2 decades.

Limitations

Our study has some inherent limitations related to its design. Information was extrapolated from reports available in the literature, and missing data were common, although attempts were made to obtain them by contacting the authors. In addition, our study collected cases from all over the world and therefore presents a heterogeneity in terms of epidemiology, risk factors, and resources available for diagnosis and treatment. Notably, up to 51.7% of cases came from Asia, predominantly India, where previous studies on mucormycosis have shown a higher risk of infection with a worse prognosis, introducing a potential bias.

Publication bias is also a limiting factor, as reports tend to describe rare or atypical disease manifestations, potentially excluding more common findings. However, this issue may be partially mitigated because we focused on SOTRs, a specific population in which cases are more likely to be reported, even if they have typical presentations.

Finally, despite the systematic search strategy, we likely still missed cases aggregated in more extensive series, including 35 SOT cases with COVID-19–associated mucormycosis published as part of a larger meta-analysis, for which only a published preprint was available at the time of the literature search, which was missed by our manual search [151].

CONCLUSIONS

Our study represents the largest description of mucormycosis among SOTRs available in current literature. We have confirmed the severity of this condition and found a significant association between its related mortality and the degree of immunosuppression experienced by the recipient, along with better-known risk factors such as diabetes and disseminated disease. Notably, we have brought attention to a previously overlooked peak in occurrences during the early posttransplant period. It is incumbent on the scientific community to embark on further investigations to validate the robustness of these findings. Specifically, there is an urgent call for comprehensive investigations, with mindful consideration for potential antifungal prophylactic regimens tailored to combat agents responsible for mucormycosis in carefully selected high-risk cases. This pursuit of additional empirical evidence will strengthen our understanding of the ailment and contribute to refining preventive measures, thereby advancing the overall care paradigm for SOTRs.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. A. L. and E. P. conceived the research question and study design; A. L., E. P., C. A., M. F., A. M., G. R., and G. V. reviewed the articles and extracted the data; H. K. and A. C. provided supplementary data on their cohort; M. C. performed the analysis; A. L., E. P., and M. C. wrote the first draft; A. G. and A. B. supervised the study; all authors contributed to and revised the submitted version of the manuscript.

Data availability. Data are available on reasonable request.

Patient consent. This study did not include factors requiring patient consent.

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

References

1. Roden MM, Zaoutis TE, Buchanan WL, et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clin Infect Dis **2005**; 41:634–53.
2. Bitar D, Lortholary O, Le Strat Y, et al. Population-based analysis of invasive fungal infections, France, 2001–2010. Emerg Infect Dis **2014**; 20:1149–55.
3. Slavin M, van Hal S, Sorrell TC, et al. Invasive infections due to filamentous fungi other than *Aspergillus*: epidemiology and determinants of mortality. Clin Microbiol Infect **2015**; 21:490.e1–e10.
4. Jeong W, Keighley C, Wolfe R, et al. The epidemiology and clinical manifestations of mucormycosis: a systematic review and meta-analysis of case reports. Clin Microbiol Infect **2019**; 25:26–34.
5. World Health Organization. WHO fungal priority pathogens list to guide research, development and public health action. **2022**. Available at: https://www.who.int/publications/i/item/9789240060241
6. Nielsen MC, Cerqueira FM, Kavuri SB, et al. Diverse clinical manifestations and challenges of mucormycosis: insights from serial cases. Open Forum Infect Dis **2023**; 10:ofad527.
7. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred Reporting Items for Systematic Reviews and Meta-analyses: the PRISMA statement. BMJ **2009**; 339:332–6.
8. De Pauw B, Walsh TJ, Donnelly JP, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis **2008**; 46:1813–21.
9. Donnelly JP, Chen SC, Kauffman CA, et al. Revision and update of the consensus definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium. Clin Infect Dis **2020**; 71:1367–76.
10. Abboud CS, Bergamasco MD, Baía CES, et al. Case report of hepatic mucormycosis after liver transplantation: successful treatment with liposomal amphotericin B followed by posaconazole sequential therapy. Transplant Proc **2012**; 44:2501–2.
11. Bakr A, Wafa E, Fouda A, et al. Successful treatment of mucormycosis in a renal allograft recipient. Clin Exp Nephrol **2008**; 12:207–10.
12. Azarpira N, Ashraf MJ, Kazemi K, Khademi B. Rhinomaxillary mucormycosis in a renal transplant recipient: case report. Exp Clin Transplant **2012**; 10:605–8.
13. Thatipelli S, Santoiemma P, Echenique IA, et al. Donor-derived renal allograft mucormycosis in a combined liver and kidney transplantation: case report and review of the literature. Transpl Infect Dis **2021**; 23:e13534.
14. Thomas S, Pawar B, Fernandes D, Nayar S, George P, Cherian S. An unusual case of pulmonary mucormycosis. Transplant Proc **2018**; 50:3943–5.
15. Tobón AM, Arango M, Fernández D, Restrepo A. Mucormycosis (zygomycosis) in a heart-kidney transplant recipient: recovery after posaconazole therapy. Clin Infect Dis **2003**; 36:1488–91.
16. Trabelsi H, Néji S, Sellami H, et al. Invasive fungal infections in renal transplant recipients: about 11 cases. J Mycol Med **2013**; 23:255–60.
17. Trasmonte MV, Jiménez JD, Santiago MÁ, et al. Association of topical amphotericin B lipid complex treatment to standard therapy for rhinomaxillary mucormycosis after liver transplantation: a case report. Transplant Proc **2012**; 44:2120–3.
18. Turnbull A, Chembo CL, Leikis M, et al. A case of pulmonary mucormycosis in a renal transplant recipient. Nephrology (Carlton) **2017**; 22:657.
19. Vahabzadeh-Hagh AM, Chao KY, Blackwell KE. Invasive oral tongue mucormycosis rapidly presenting after orthotopic liver transplant. Ear Nose Throat J **2019**; 98:268–70.
20. Hofman V, Dhouibi A, Butori C, et al. Usefulness of molecular biology performed with formaldehyde-fixed paraffin embedded tissue for the diagnosis of combined pulmonary invasive mucormycosis and aspergillosis in an immunocompromised patient. Diagn Pathol **2010**; 5:1.
21. Ville S, Talarmin JP, Gaultier-Lintia A, et al. Disseminated mucormycosis with cerebral involvement owing to *Rhizopus microsporus* in a kidney recipient treated with combined liposomal amphotericin B and posaconazole therapy. Exp Clin Transplant **2016**; 14:96–9.
22. Vondran FWR, Knitsch W, Krech T, et al. Intestinal mucormycosis with *Rhizopus microsporus* after liver transplantation—successful treatment of a rare but life-threatening complication. Transplantation **2014**; 97:e11–3.
23. Geramizadeh B, Kazemi K, Shamsaifar AR, Bahraini A, Nikeghbalian S, Malekhosseini SA. Isolated renal mucormycosis after liver transplantation: an unusual case report. Iran Red Crescent Med J **2012**; 14:447–50.
24. Webb BJ, Blair JE, Kusne S, et al. Concurrent pulmonary *Aspergillus fumigatus* and mucor infection in a cardiac transplant recipient: a case report. Transplant Proc **2013**; 45:792–7.
25. Yetmar ZA, Lahr B, Brumble L, et al. Epidemiology, risk factors, and association of antifungal prophylaxis on early invasive fungal infection in heart transplant recipients. Transpl Infect Dis **2021**; 23:e13714.
26. Yu Z, Theodosakis N, Fitzpatrick MJ, Foreman RK, Mackool B. A 39-year-old male congenital tricuspid atresia patient who presented with a new axillary lesion after an orthotopic heart transplant. Dermatopathol (Basel) **2019**; 6:220–4.
27. Zhang R, Zhang JW, Szerlip HM. Endocarditis and hemorrhagic stroke caused by *Cunninghamella bertholletiae* infection after kidney transplantation. Am J kidney Dis **2002**; 40:842–6.
28. Zhang Q, Liu H, Qiu S, et al. A rare case of pulmonary coinfection by *Lichtheimia ramosa* and *Aspergillus fumigatus* in a patient with delayed graft function after renal transplantation. Transplant Proc **2019**; 51:551–5.
29. Zhao L, Wang CX, Zhang L, et al. Mucormycosis extending from the surgical wound to the transplanted kidney: case report and literature review. Exp Clin Transplant **2012**; 10:403–5.
30. Bardwell J, Youseffi B, Marquez J, Zangeneh TT, Al-Obaidi M. Pulmonary mucormycosis in a heart transplant patient. Am J Med **2020**; 133:e524–5.
31. Belliere J, Rolland M, Tournier E, et al. Early necrotic skin lesions after a ABO-incompatible kidney transplantation: the threat of *Cunninghamella* spp. Transpl Infect Dis **2019**; 21:e13173.
32. Berktaş B, Taşkapan H, Bayindir T, Kayabas U, Yildirim IO. Mucormycosis presented with facial pain in a renal transplant patient: a case report. Transplant Proc **2019**; 51:2498–500.
33. Brugière O, Dauriat G, Mal H, et al. Pulmonary mucormycosis (zygomycosis) in a lung transplant recipient: recovery after posaconazole therapy. Transplantation **2005**; 80:1361–2.
34. Lin CT, Lee JC, Chan DC, Yu JC, Hsieh CB. Successful treatment of mucormycosis infection after liver transplantation: report of a case and review of the literature. Z Gastroenterol **2011**; 49:449–51.
35. Chaudhary RJ, Choudhary NS, Saraf N, et al. Delayed graft dysfunction due to invasive hepatic mucormycosis after living donor liver transplantation. J Clin Exp Hepatol **2020**; 10:629–32.
36. Chitsaz S, Bagheri J, Mandegar MH, Rayatzadeh H, Razavi J, Azadi L. Extensive sino-orbital zygomycosis after heart transplantation: a case report. Transplant Proc **2009**; 41:2927–9.
37. Clauss H, Samuel R. Simultaneous mold infections in an orthotopic heart transplant recipient. Transpl Infect Dis **2008**; 10:343–5.
38. Aggarwal P, Patel H, Gonzalez L, Brown L, Agarwal A, Speeg K. Invasive colonic mucormycosis in an immunocompromised postliver transplant patient. ACG Case Reports J **2020**; 7:e00450.
39. Colón-Santos E, González-Ramos M, Bertrán-Pasarell J, Rodríguez-Vega G, Almira-Suarez M, Vélez-Rosario R. Disseminated nocardiosis masking an atypical zygomycosis presentation in a kidney transplant recipient. Transpl Infect Dis **2011**; 13:380–4.
40. Quinio D, Karam A, Leroy JP, et al. Zygomycosis caused by *Cunninghamella bertholletiae* in a kidney transplant recipient. Med Mycol **2004**; 42:177–80.
41. Dantis K, Rathore V, Kashyap NK, Gupta N, De S, Singha SK. SARS-CoV-2 sequel: pulmonary mucormycosis with a mycotic aneurysm in a transplant recipient. Tuberc Respir Dis (Seoul) **2021**; 84:335–7.
42. Cooke DT, Pagani FD, Kaul DR, et al. Successful treatment of pulmonary zygomycosis in two transplant recipients with liposomal amphotericin B and partial surgical resection followed by posaconazole. Mycoses **2010**; 53:163–7.
43. Davuodi S, Manshadi SAD, Salehi MR, Yazdi F, Khazravi M, Fazli JT. Fatal cutaneous mucormycosis after kidney transplant. Exp Clin Transplant **2015**; 13:82–5.
44. Deyo JC, Nicolsen N, Lachiewicz A, Kozlowski T. Salvage treatment of mucormycosis post-liver transplant with posaconazole during sirolimus maintenance immunosuppression. J Pharm Pract **2017**; 30:261–5.
45. Do GW, Jung SW, Jun JB, Seo JH, Nah YW. Colonic mucormycosis presented with ischemic colitis in a liver transplant recipient. World J Gastroenterol **2013**; 19:3508–11.
46. Echo A, Hovsepian RV, Shen GK. Localized cecal zygomycosis following renal transplantation. Transpl Infect Dis **2005**; 7:68–70.
47. Damaraju V, Agarwal R, Dhooria S, et al. Pulmonary mucormycosis (zygomycosis) in a lung transplant recipient: recovery after posaconazole therapy. Transpl Infect Dis **2010**; 12:206–9.
48. Farojov R, Aydın O, Yılmaz C, et al. Rhino-orbita-maxillary mucormycosis after liver transplantation: a case report. Transplant Proc **2016**; 48:3210–3.

49. Chua AP, Billings SD, Budev MM, Mehta AC. Ulcerative leg nodules in a transplant recipient. Cleve Clin J Med **2009**; 76:575–6, 616.
50. Lakshminarayana G, Rajesh R, Kurian G, Unni VN. Zygomycosis in a renal allograft recipient. Indian J Nephrol **2009**; 19:30–3.
51. Vetrone G, Grazi GL, Ercolani G, et al. Successful treatment of rhinomaxillary form of mucormycosis infection after liver transplantation: a case report. Transplant Proc **2006**; 38:1445–7.
52. Gani I, Doroodchi A, Falkenstrom K, et al. Gastric mucormycosis in a renal transplant patient treated with isavuconazole monotherapy. Case Rep Transplant **2019**; 2019:9839780.
53. Gaut D, Cone BD, Gregson AL, Agopian VG. Gastrointestinal mucormycosis after orthotopic liver transplantation presenting as femoral nerve palsy: a case report and review of the literature. Transplant Proc **2017**; 49:1608–14.
54. Gupta A, Jain S, Agrawal C, Kapoor G. Successful outcome of mucormycosis in two children on induction therapy for acute lymphoblastic leukemia. Indian J Med Paediatr Oncol **2013**; 34:313–6.
55. Gurevich M, Levi I, Steinberg R, et al. Mucormycosis in a liver allograft: salvage re-transplantation and targeted immunosuppressive management. Transpl Infect Dis **2012**; 14:E97–101.
56. Hatahet MH, Narayanan M, Cleaves C, Zreik R. Disseminated mucormycosis in a patient with recent kidney transplantation: a case report and review of the literature. Case Rep Nephrol Urol **2013**; 3:58–63.
57. Zhang H, Wang K, Chen H, et al. The double-edged sword of immunosuppressive therapy in kidney transplantation: a rare case report of pulmonary mucormycosis post-transplant and literature review. Front Med **2020**; 7:500.
58. Hoang S, Sestito M. A rare presentation of ileocecal mucormycosis in a heart transplant recipient. ACG Case Reports J **2021**; 8:e00699.
59. Hunt WR. Pulmonary mucormycosis in a patient with poorly controlled diabetes after a liver transplant. Am J Med Sci **2017**; 354:e1.
60. Alfano G, Fontana F, Francesca D, et al. Gastric mucormycosis in a liver and kidney transplant recipient: case report and concise review of literature. Transplant Proc **2018**; 50:905–9.
61. Haque H, Nettboy S, Kumar S. Surgical-site mucormycosis infection in a solid-organ transplant recipient and a concise review of the literature. BMJ Case Rep **2019**; 12:e229687.
62. Irtan S, Lamerain M, Lesage F, et al. Mucormycosis as a rare cause of severe gastrointestinal bleeding after multivisceral transplantation. Transpl Infect Dis **2013**; 15:E235–8.
63. Kawaji-Kanayama Y, Nishimura A, Yasuda M, et al. Chronic invasive fungal rhinosinusitis with atypical clinical presentation in an immunocompromised patient. Infect Drug Resist **2020**; 13:3225–32.
64. Kerbaul F, Guidon C, Collart F, et al. Abdominal wall mucormycosis after heart transplantation. J Cardiothorac Vasc Anesth **2004**; 18:822–3.
65. Khatri A, Chang KM, Berlinrut I, Wallach F. Mucormycosis after coronavirus disease 2019 infection in a heart transplant recipient—case report and review of literature. J Mycol Med **2021**; 31:101125.
66. Kulkarni MJ, Dsouza A, Pramod GR, et al. Combined aspergillus and mucormycosis infection in a renal allograft recipient—a case report. Indian J Transplant **2020**; 14:260–2.
67. Lai MC, Zhang W, Yang Z, et al. First case report of isolated penile mucormycosis in a liver transplantation recipient. Int J Infect Dis **2014**; 29:208–10.
68. Lango-Maziarz A, Kolaczkowska M, Siondalski P, Duda M, Dubowik M, Lango R. Colon mucormycosis with renal spread resistant to lipid complex amphotericin and isavuconazole treatment in a heart transplant recipient. Polish Arch Intern Med **2022**; 132:16156.
69. Łanocha AA, Guzicka-Kazimierczak R, Zdziarska B, Wawrzynowicz-Syczewska M. Mucormycosis in a patient with acute myeloblastic leukemia following liver transplantation for Wilson's disease. Ann Agric Environ Med **2019**; 26:665–8.
70. Nichols L, Ocque RZ, Daly I. Zygomycosis associated with HIV infection and liver transplantation. Patholog Res Int **2011**; 2011:545981.
71. Alkhunaizi AM, Amir AA, Al-Tawfiq JA. Invasive fungal infections in living unrelated renal transplantation. Transplant Proc **2005**; 37:3034–7.
72. Li X, Ren H, Li M, Zhang L, Yang B, Zhang W. Pulmonary mucormycosis after heart-kidney transplantation treated with vats lobectomy: a case report. Int J Clin Exp Med **2018**; 11:12790–5.
73. Liapis CD, Petrikkos GL, Paraskevas KI, et al. External Iliac artery stent mucormycosis in a renal transplant patient. Ann Vasc Surg **2006**; 20:253–7.
74. Ashkenazi-Hoffnung L, Bilavsky E, Avitzur Y, Amir J. Successful treatment of cutaneous zygomycosis with intravenous amphotericin B followed by oral posaconazole in a multivisceral transplant recipient. Transplantation **2010**; 90:1133–5.
75. Doan L, Al-Khafaji A. Zygomycosis-Induced rash after liver transplant. Am J Gastroenterol **2017**; 112:533.
76. Kwan LPY, Choy CBY, Chan TM, Suen WS, Yap DYH. Successful treatment of pulmonary *Rhizopus* infection with surgical resection and posaconazole in a renal transplant recipient. Nephrology (Carlton) **2013**; 18:74–5.
77. Louis-Auguste JR, Micallef C, Ambrose T, et al. Fatal breakthrough mucormycosis in a multivisceral transplant patient receiving micafungin: case report and literature review. IDCases **2018**; 12:76–9.
78. Manchikalapati P, Canon CL, Jhala N, Eloubeidi MA. Gastrointestinal zygomycosis complicating heart and lung transplantation in a patient with Eisenmenger's syndrome. Dig Dis Sci **2005**; 50:1181–3.
79. Margoles L, DeNofrio D, Patel AR, et al. Disseminated mucormycosis masquerading as rejection early after orthotopic heart transplantation. Transpl Infect Dis **2018**; 20:e12820.
80. McGuire FR, Grinnan DC, Robbins M. Mucormycosis of the bronchial anastomosis: a case of successful medical treatment and historic review. J Hear lung Transplant **2007**; 26:857–61.
81. Meena S, Singh G, Pandey M, Xess I. Exophiala jeanselmei and *Rhizopus* oryzae co-infection post renal transplant. J Clin Diagnostic Res **2019**; 13:DD01–3.
82. Allam SR, Madhrira MM, Memon IA, et al. Invasive mucormycosis in a renal transplant recipient. Kidney Int **2020**; 97:216.
83. Meshram HS, Kumar D, Kute VB. Rare and unusual follow-up sequelae of coronavirus disease 2019: splenic mucormycosis in a renal transplant recipient. Transplant Proc **2022**; 54:1554–6.
84. Martin MS, Smith AA, Lobo M, Paramesh AS. Successful treatment of recurrent pulmonary mucormycosis in a renal transplant patient: a case report and literature review. Case Rep Transplant **2017**; 2017:1925070.
85. Mysorekar VV, Rao SG. Cytomegalovirus pneumonia with pulmonary mucormycosis. Indian J Pathol Microbiol **2008**; 51:294–5.
86. Naik CA, Mathai SK, Sandkovsky US, et al. Acute myocardial infarction secondary to mucormycosis after lung transplantation. IDCases **2021**; 23:e01019.
87. Nalmas S, Bishburg E, Goldstein C. Mucormycosis in a transplanted kidney. Transpl Infect Dis **2008**; 10:269–71.
88. Nam Y, Jung J, Park SS, et al. Disseminated mucormycosis with myocardial involvement in a renal transplant recipient. Transpl Infect Dis **2015**; 17:890–6.
89. Nandwani A, Jha PK, Duggal R, Kher V. Invasive gastric mucormycosis and cytomegalovirus infection in an ABO incompatible renal transplant recipient. Indian J Nephrol **2015**; 25:373–6.
90. Nautiyal A, Gadde A, Mahapatra AK, Bansal SB. A case report of central nervous system mucormycosis and aspergillus pneumopericardium in a renal transplant recipient. Indian J Transplant **2020**; 14:360–2.
91. Navanukroh O, Jitmuang A, Chayakulkeeree M, Ngamskulrungroj P. Disseminated *Cunninghamella bertholletiae* infection with spinal epidural abscess in a kidney transplant patient: case report and literature review. Transpl Infect Dis **2014**; 16:658–65.
92. Nokes BT, Pajaro O, Stephen J, et al. Monster lung cavity in a heart transplant recipient. Heart Surg Forum **2018**; 21:E072–4.
93. Miladipour A, Ghanei E, Nasrollahi A, Moghaddasi H. Successful treatment of mucormycosis after kidney transplantation. Iran J Kidney Dis **2008**; 2:163–6.
94. Turan MN, Tatar E, Yaprak M, et al. A mucormycosis case presented with orbital apex syndrome and hemiplegia in a renal transplant patient. Int Urol Nephrol **2013**; 45:1815–9.
95. Page AV, Evans AJ, Snell L, Liles WC. Primary cutaneous mucormycosis in a lung transplant recipient: case report and concise review of the literature. Transpl Infect Dis **2008**; 10:419–25.
96. Parikh A, Tuli A, Sridhar FK, Mammen K. Mucormycosis in the post renal transplant surgical scar. Indian J Transplant **2015**; 9:116–8.
97. Park W, Jang M, Hwang E, et al. Allograft mucormycosis due to *Rhizopus microsporus* in a kidney transplant recipient. Transplant Proc **2014**; 46:623–5.
98. Patel A, Bishburg E, Nagarakanti S. Mucormycosis in an HIV-infected renal transplant patient: a case report and review of the literature. Am J Case Rep **2014**; 15:74–8.
99. Gallet P, Debourgogne A, Rivier A, et al. Successful management of rhinosinusal zygomycosis in a renal transplant recipient. Mycoses **2011**; 54:e593–8.
100. Pedemonte-Sarrias G, Gras-Cabrerizo JR, Rodríguez-Álvarez F, Montserrat-Gili JR. Rhinocerebral mucormycosis in a 5-month heart transplant recipient. J Oral Maxillofac Pathol **2015**; 19:375–8.
101. Petrochko JM, Abrahamian G, Cigarroa F, Thomas E. Colonic mucormycosis in solid organ transplantation: case report and review of the literature (colonic mucormycosis after DDLT). Transpl Infect Dis **2020**; 22:e13362.
102. Prasad N, Ram R, Satti Reddy V, Dakshinamurty KV. Non-fatal gastric mucormycosis in a renal transplant patient and review of the literature. Transpl Infect Dis **2006**; 8:237–41.
103. Quiñónez ZA, Speicher JT, Sebat C, Avdalovic M. Cutaneous *Rhizopus* infection at a central venous catheter site in a critically ill renal transplant patient. Healthc Infect **2012**; 17:83–6.

104. Arana C, Cuevas Ramírez RE, Xipell M, et al. Mucormycosis associated with COVID-19 in two kidney transplant patients. Transpl Infect Dis **2021**; 23:e13652.
105. Rajagopal K, Watkins AC, Gibber M, et al. Reoperative lung transplantation for donor-derived pulmonary mucormycosis. Ann Thorac Surg **2014**; 98:327–9.
106. Ram R, Swarnalatha G, Naidu GD, Kaligotla DV. Multiple ring enhancing lesions in brain due to disseminated zygomycosis in a renal transplant recipient. Nephrology (Carlton) **2013**; 18:479–80.
107. Ramos A, Cuervas-Mons V, Noblejas A, et al. Breakthrough rhinocerebral mucormycosis in a liver transplant patient receiving caspofungin. Transplant Proc **2009**; 41:1972–5.
108. Rasiah S, Fernandes KD, Sajiv CT, Pawar B. A case of fatal disseminated *Apophysomyces elegans* infection in a renal allograft recipient. Indian J Nephrol **2014**; 24:54–6.
109. Dos Reis FP, Campos SV, Aiello VD, Duarte MIS, Samano MN, Pego-Fernandes PM. Gastrointestinal mucormycosis post lung transplantation. Brazilian J Infect Dis **2019**; 23:368–70.
110. Rrapi R, Chand S, Gaffney R, et al. Cutaneous mucormycosis arising in the skin folds of immunocompromised patients: a case series. JAAD Case Rep **2021**; 17:92–5.
111. Sabhapandit S, Sharma M, Sekaran A, et al. Postliver transplantation rhino-orbital mucormycosis, an unexpected cause of a downhill course. Case Reports Hepatol **2022**; 2022:5413315.
112. Salehi E, Hedayati MT, Zoll J, et al. Discrimination of aspergillosis, mucormycosis, fusariosis, and scedosporiosis in formalin-fixed paraffin-embedded tissue specimens by use of multiple real-time quantitative PCR assays. J Clin Microbiol **2016**; 54:2798–803.
113. Saxena S, Sharma S, Bansal R, Kulkarni SB. Unusual presentation of mucormycosis. Indian J Transplant **2016**; 10:52–4.
114. Mills SEA, Yeldandi AV, Odell DD. Surgical treatment of multifocal pulmonary mucormycosis. Ann Thorac Surg **2018**; 106:e93–5.
115. Asabeh EA, Zeer ZMM, Dukmak ON, Al Mohtasib ME, Asbeh YA. Pulmonary mucormycosis after renal transplantation: a case report and a literature review. Ann Med Surg **2022**; 78:103889.
116. Ghaderkhani S, Ahmadinejad Z, Dashti H, Safaei M, Ghiasvand F. Wound infection with an unusual pathogen after liver transplantation. Case Rep Transplant **2020**; 2020:8396507.
117. Schneider M, Kobayashi K, Uldry E, Demartines N, Golshayan D, Halkic N. *Rhizomucor* hepatosplenic abscesses in a patient with renal and pancreatic transplantation. Ann R Coll Surg Engl **2021**; 103:e131–5.
118. Gökbulut Bektaş Ş, Kandemir AB, Ayaz ÇM, Yilmaz AN, İzdeş S. COVID-19–related rhino-orbital-cerebral mucormycosis in a renal transplant recipient. Exp Clin Transplant **2022**; 20:213–7.
119. Sethi P, Balakrishnan D, Surendran S, Mohamed ZU. Fulminant zygomycosis of graft liver following liver transplantation. BMJ Case Rep **2016**; 2016:bcr2015214097.
120. Sharma D, Dahal K, Pathak B, Dahal U. Case of early-disseminated *Rhizopus microsporus* var *microsporus* mucormycosis in a renal transplant patient. Int Med Case Rep J **2016**; 9:139–43.
121. Singh N, Gayowski T, Singh J, Yu VL. Invasive gastrointestinal zygomycosis in a liver transplant recipient: case report and review of zygomycosis in solid-organ transplant recipients. Clin Infect Dis **1995**; 20:617–20.
122. Spithoven EM, Bruns AHW, Petri BJ, et al. Renal transplant patient survives a donor-derived abdominal invasive mucormycosis (*Lichtheimia ramosa*). Med Mycol Case Rep **2020**; 30:39–42.
123. Iida T, Sawada N, Takahashi M, et al. Successful treatment of invasive mucormycosis in a liver transplant patient by arm amputation. Transplant Proc **2010**; 42: 2794–6.
124. Talebi-Taher M, Alavi Niakou SN, Javad-Mousavi SA, Vaziri M, Iranpour A, Dehghani M. Pulmonary mucormycosis in a patient with chronic rejection of kidney transplant: a case report. Tanaffos **2015**; 14:149–52.
125. Tan M, Gibney EM. Lung mass in a kidney transplant recipient. Am J Transplant **2015**; 15:281–2.
126. Ganesh K, Abraham M, Kumar J, Simon S. Invasive fungal diseases in renal transplantation—case series. Indian J Transplant **2021**; 15:169–75.
127. García-Pajares F, Sánchez-Antolín G, Almohalla Alvárez C, et al. Cutaneous mucormycosis infection by *Absidia* in two consecutive liver transplant patients. Transplant Proc **2012**; 44:1562–4.
128. Hill MC, Belkin MN, McMullen P II, et al. Management of pulmonary mucormycosis after orthotopic heart transplant: a case series. Transplant Proc **2021**; 53: 3051–5.
129. Uçkay I, Chalandon Y, Sartoretti P, et al. Invasive zygomycosis in transplant recipients. Clin Transplant **2007**; 21:577–82.
130. Tayyebi N, Amouian S, Mohamadian N, Rahimi HR. Renal allograft mucormycosis: report of two cases. Surg Infect (Larchmt) **2007**; 8:535–8.
131. Woo PCY, Lau SKP, Ngan AHY, et al. *Lichtheimia hongkongensis* sp nov, a novel *Lichtheimia* spp associated with rhinocerebral, gastrointestinal, and cutaneous mucormycosis. Diagn Microbiol Infect Dis **2010**; 66:274–84.
132. Zhu X, Liu H, Wang W, et al. Two cases of transplant renal artery thrombosis and spontaneous rupture caused by mucormycosis. Transpl Infect Dis **2015**; 17:442–8.
133. Meshram HS, Kute VB, Chauhan S, Desai S. Mucormycosis in post-COVID-19 renal transplant patients: a lethal complication in follow-up. Transpl Infect Dis **2021**; 23:e13663.
134. Jiménez C, Lumbreras C, Aguado JM, et al. Successful treatment of mucor infection after liver or pancreas-kidney transplantation. Transplantation **2002**; 73: 476–80.
135. Stelzmueller I, Lass-Floerl C, Geltner C, et al. Zygomycosis and other rare filamentous fungal infections in solid organ transplant recipients. Transpl Int **2008**; 21:534–46.
136. Neto FMFD, Camargo PCLB, Costa AN, et al. Fungal infection by Mucorales order in lung transplantation: 4 case reports. Transplant Proc **2014**; 46:1849–51.
137. Eubank TA, Mobley CM, Moaddab M, et al. Successful treatment of invasive mucormycosis in orthotopic liver transplant population. Case Rep Transplant **2021**; 2021:8667589.
138. Patel A, Kaur H, Xess I, et al. A multicentre observational study on the epidemiology, risk factors, management and outcomes of mucormycosis in India. Clin Microbiol Infect **2020**; 26:944.e9–15.
139. Lim LL, Lau ESH, Fu AWC, et al. Effects of a technology-assisted integrated diabetes care program on cardiometabolic risk factors among patients with type 2 diabetes in the Asia-pacific region: the JADE program randomized clinical trial. JAMA Netw Open **2021**; 4:e217557.
140. Yuan C, Wang X, Pecoraro L. Environmental factors shaping the diversity and spatial-temporal distribution of indoor and outdoor culturable airborne fungal communities in Tianjin university campus, Tianjin, China. Front Microbiol **2022**; 13:928921.
141. World Health Organization. WHO Global Observatory on Donation and Transplantation. **2021**. Available at: https://www.transplant-observatory.org/. Accessed September 2023.
142. Lentine KL, Smith JM, Hart A, et al. OPTN/SRTR 2020 annual data report: kidney. Am J Transplant **2022**; 22(suppl 2):21–136.
143. Gloor J, Stegall MD. Sensitized renal transplant recipients: current protocols and future directions. Nat Rev Nephrol **2010**; 6:297–306.
144. Park Y, Ko EJ, Chung BH, Yang CW. Kidney transplantation in highly sensitized recipients. Kidney Res Clin Pract **2021**; 40:355–70.
145. Oweira H, Ramouz A, Ghamarnejad O, et al. Risk factors of rejection in renal transplant recipients: a narrative review. J Clin Med **2022**; 11:1392.
146. Fishman JA. Infection in solid-organ transplant recipients. N Engl J Med **2007**; 357:2601–14.
147. Cornely OA, Alastruey-Izquierdo A, Arenz D, et al. Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium. Lancet Infect Dis **2019**; 19:e405–21.
148. Perfect JR, Klotman ME, Gilbert CC, et al. Prophylactic intravenous amphotericin B in neutropenic autologous bone marrow transplant recipients. J Infect Dis **1992**; 165:891–7.
149. Lorf T, Braun F, Rüchel R, Müller A, Sattler B, Ringe B. Systemic mycoses during prophylactical use of liposomal amphotericin B (Ambisome) after liver transplantation. Mycoses **1999**; 42(1–2):47–53.
150. Spellberg B, Ibrahim A, Roilides E, et al. Combination therapy for mucormycosis: why, what, and how? Clin Infect Dis **2012**; 54:S73–8.
151. Özbek L, Topçu U, Manay M, et al. COVID-19–associated mucormycosis: a systematic review and meta-analysis of 958 cases. Clin Microbiol Infect **2023**; 29: 722–31.

Dovato
dolutegravir/lamivudine

EVIDENCE SUPPORTS THE HIGH BARRIER TO RESISTANCE OF DOVATO UP TO 5 YEARS[1-3]

CONFIDENCE IN DOVATO ACROSS TREATMENT SETTINGS[4–9]

Treatment-naïve resistance rates, with up to **3 years of evidence**[5–7]

0% (n=0/1,885)*,[4]
REAL-WORLD EVIDENCE

0.1% (n=1/953)**,†,‡,§,5–7
RANDOMISED CONTROLLED TRIALS

Treatment-experienced resistance rates, with up to **5 years of evidence**[1–3]

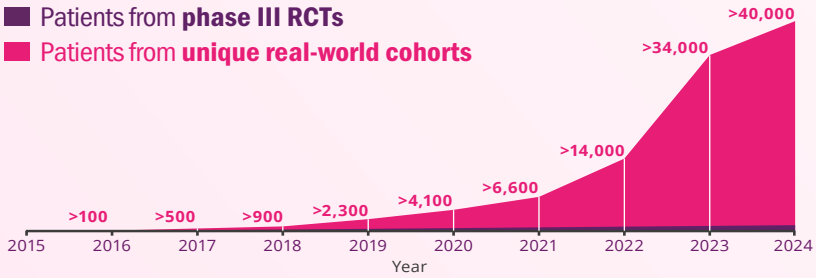
0.03% (n=10/35,888)*,[4]
REAL-WORLD EVIDENCE

0% (n=0/615)||,¶,#,8,9
RANDOMISED CONTROLLED TRIALS

>300,000 PEOPLE LIVING WITH HIV HAVE BEEN TREATED WITH DOVATO GLOBALLY[10]

DOVATO is supported by a wealth of evidence, with the outcomes of **>40,000** people living with HIV captured within clinical trials and real-world evidence, including those with:[4–9,11,12]

- **NO PRIOR TREATMENT EXPERIENCE**[13]
- **NO BASELINE RESISTANCE TESTING**[13]
- **HIGH BASELINE VIRAL LOAD** (>100,000 copies/mL and even >1M copies/mL)[6,13]
- **LOW CD4 + COUNT** (≤200 cells/mm³)[13]



IS IT TIME TO RECONSIDER THE VALUE OF THE 2ND NRTI?

LEARN MORE

DOVATO is indicated for the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in adults and adolescents above 12 years of age weighing at least 40 kg, with no known or suspected resistance to the integrase inhibitor class, or lamivudine.[13]

Adverse events should be reported. Reporting forms and information can be found at **https://yellowcard.mhra.gov.uk/** or search for MHRA Yellowcard in the Google Play or Apple App store. Adverse events should also be reported to GSK on 0800 221441

REFERENCES

1. Maggiolo F et al. BMC Infect Dis 2022; 22(1): 782.
2. Taramasso L et al. AIDS Patient Care STDS 2021; 35(9): 342–353.
3. Ciccullo A et al. JAIDS 2021; 88(3): 234–237.
4. ViiV Healthcare. Data on File. REF-223795. 2024.
5. Cahn P et al. AIDS 2022; 36(1): 39–48.
6. Rolle C et al. Open Forum Infect Dis 2023; 10(3): ofad101.
7. Cordova E et al. Poster presented at 12th IAS Conference on HIV Science. 23–26 July 2023. Brisbane, Australia. TUPEB02.
8. De Wit S et al. Slides presented at HIV Glasgow. 23–26 October 2022. Virtual and Glasgow, UK. M041.
9. Llibre J et al. Clin Infect Dis 2023; 76(4): 720–729.
10. ViiV Healthcare. Data on File. REF-220949. 2024.
11. Rolle C et al. Poster presented IDWeek. 11–15 October 2023. Virtual and Boston, USA. 1603.
12. Slim J et al. Abstract presented IDWeek. 11–15 October 2023. Virtual and Boston, USA. 1593.
13. DOVATO. Summary of Product Characteristics. June 2023.

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ABBREVIATIONS

3TC, lamivudine; **CD4,** cluster of differentiation 4; **DTG,** dolutegravir; **FDA,** United States Food and Drug Administration; **FTC,** emtricitabine; **HIV,** human immunodeficiency virus; **ITT-E,** intention-to-treat exposed; **NRTI,** nucleoside/nucleotide reverse transcriptase inhibitor; **RCT,** randomised controlled trial; **RNA,** ribonucleic acid; **TAF,** tenofovir alafenamide fumarate; **TDF,** tenofovir disoproxil fumarate; **XTC,** emtricitabine.

FOOTNOTES

*Data extracted from a systematic literature review of DTG+3TC real-world evidence. Overlap between cohorts cannot be fully excluded.

**The reported rate reflects the sum-total of resistance cases calculated from GEMINI I and II (n=1/716, through 144 weeks), STAT (n=0/131, through 52 weeks), and D2ARLING (n=0/106, through 24 weeks).[5–7]

†GEMINI I and II are two identical 148-week, phase III, randomised, double-blind, multicentre, parallel-group, non-inferiority, controlled clinical trials testing the efficacy of DTG/3TC in treatment-naïve patients. Participants with screening HIV-1 RNA ≤500,000 copies/mL were randomised 1:1 to once-daily DTG/3TC (n=716, pooled) or DTG + TDF/FTC (n=717, pooled). The primary endpoint of each GEMINI study was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 48 (ITT-E population, snapshot algorithm).[13]

‡STAT is a phase IIIb, open-label, 48-week, single-arm pilot study evaluating the feasibility, efficacy, and safety of DTG/3TC in 131 newly diagnosed HIV-1 infected adults as a first line regimen. The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 24.[6]

§D2ARLING is a randomised, open-label, phase IV study designed to assess the efficacy and safety of DTG/3TC in treatment-naïve people with HIV with no available baseline HIV-1 resistance testing. Participants were randomised in a 1:1 ratio to receive DTG/3TC (n=106) or DTG + TDF/XTC (n=108). The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 48.[7] Results at week 24 of the study.

||The reported rate reflects the sum-total of resistance cases calculated from TANGO (n=0/369, through 196 weeks) and SALSA (n=0/246, through 48 weeks).[8,9]

¶TANGO is a randomised, open-label, trial testing the efficacy of DOVATO in virologically suppressed patients. Participants were randomised in a 1:1 ratio to receive DOVATO (n=369) or continue with TAF-containing regimens (n=372) for up to 200 weeks. At Week 148, 298 of those on TAF-based regimens switched to DOVATO. The primary efficacy endpoint was the proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL (virologic non-response) as per the FDA Snapshot category at Week 48 (adjusted for randomisation stratification factor).[8,13]

#SALSA is a phase III, randomised, open-label, non-inferiority clinical trial evaluating the efficacy and safety of switching to DTG/3TC compared with continuing current antiretroviral regimens in virologically suppressed adults with HIV. Eligible participants were randomised 1:1 to switch to once-daily DTG/3TC (n=246) or continue current antiretroviral regimens (n=247). The primary endpoint was the proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL at Week 48 (ITT-E population, snapshot algorithm).[9]

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